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Psychotic Disorders in *DSM-III-R*

By Kenneth S. Kendler, Robert L. Spitzer, and Janet B.W. Williams

Neurochemical Abnormalities of Anorexia Nervosa and Bulimia Nervosa

By Maurizio Fava, Paul M. Copeland, Ulrich Schweiger, et al.

Psychiatric Aspects of Organ Transplantation

By Owen S. Surman

Official Journal of the American Psychiatric Association

Her anxiolytic is working—but she's alert, functioning, and at no risk of a benzodiazepine withdrawal syndrome when therapy ends.

BuSpar® (buspirone HCl)

References: 1. Rickels K, et al: Buspirone and diazepam in anxiety: A controlled study. *J Clin Psychiatry* 1982;43(12, Sec 2):81-86. **2.** Newton RE, et al: A review of the side effect profile of buspirone. *Am J Med* 1986;80(suppl 3B):17-21. **3.** Lucki I, et al: Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. *Br J Clin Pharmacol* 1987;23:207-211. **4.** Lader M: Assessing the potential for buspirone dependence or abuse and effects of its withdrawal. *Am J Med* 1987;82(suppl 5A):20-26.

Contraindications: Hypersensitivity to buspirone hydrochloride.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: *General*—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (eg, dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported; the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic ef (ie, represent akathisia).

***Information for Patients*—**Patients should be instructed to inform their physician about any medicatio prescription or nonprescription, alcohol or drugs they are now taking or plan to take during treatment with spirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregn while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate tentially dangerous machinery until they experience how this medication affects them.

***Drug Interactions*—**Concomitant use with other CNS active drugs should be approached with caution **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in patients. Concomitant administration of BuSpar and haloperidol resulted in increased serum haloperidol centrations in normal volunteers. The clinical significance is not clear. Buspirone does not displace tig bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less fir bound drugs like digoxin. However, there was one report of prolonged prothrombin time when buspirone given to a patient also treated with warfarin, phenytoin, phenobarbital, digoxin, and Synthroid.

***Carcinogenesis, Mutagenesis, Impairment of Fertility*—**No evidence of carcinogenic potential observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chrom somal aberrations or abnormalities did not occur.

***Pregnancy: Teratogenic Effects*—**Pregnancy Category B: Should be used during pregnancy only clearly needed.

***Nursing Mothers*—**Administration to nursing women should be avoided if clinically possible.

***Pediatric Use*—**The safety and effectiveness have not been determined in individuals below 18 years of a

***Use in the Elderly*—**No unusual, adverse, age-related phenomena have been identified in elderly patie receiving a total, modal daily dose of 15 mg.

***Use in Patients with Impaired Hepatic or Renal Function*—**Since buspirone is metabolized by liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): *Commonly Observed*—The more commonly obser untoward events, not seen at an equivalent incidence in placebo-treated patients, include dizziness, naus headache, nervousness, lightheadedness, and excitement.

***Associated with Discontinuation of Treatment*—**The more common events causing discontinuation

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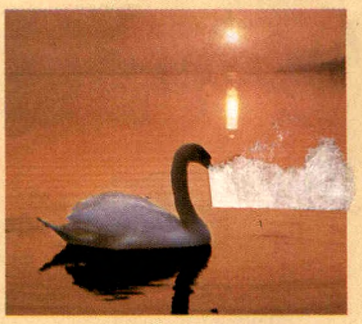

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The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness (12%), nausea (8%), headache (6%), nervousness (5%), lightheadedness (3%), and excitement (2%).

*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

P, 24, 368.

cluded: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Premarketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: non-specific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances; infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding; rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Postintroduction Clinical Experience—Rare occurrences of allergic reactions, cogwheel rigidity, dystonic reactions, ecchymosis, emotional lability, tunnel vision, and urinary retention have been reported. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to BuSpar has not been determined.

Drug Abuse and Dependence: *Controlled Substance Class*—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: *Signs and Symptoms*—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

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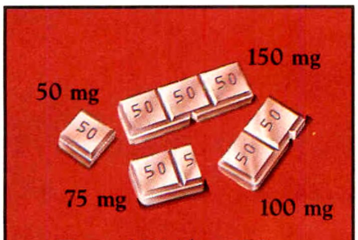

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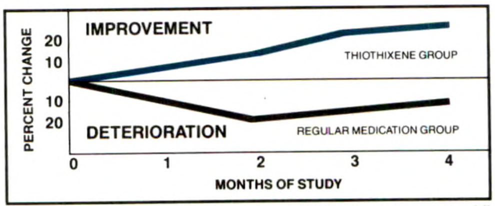

(Adapted from DiMascio and Demirgian[2,3])

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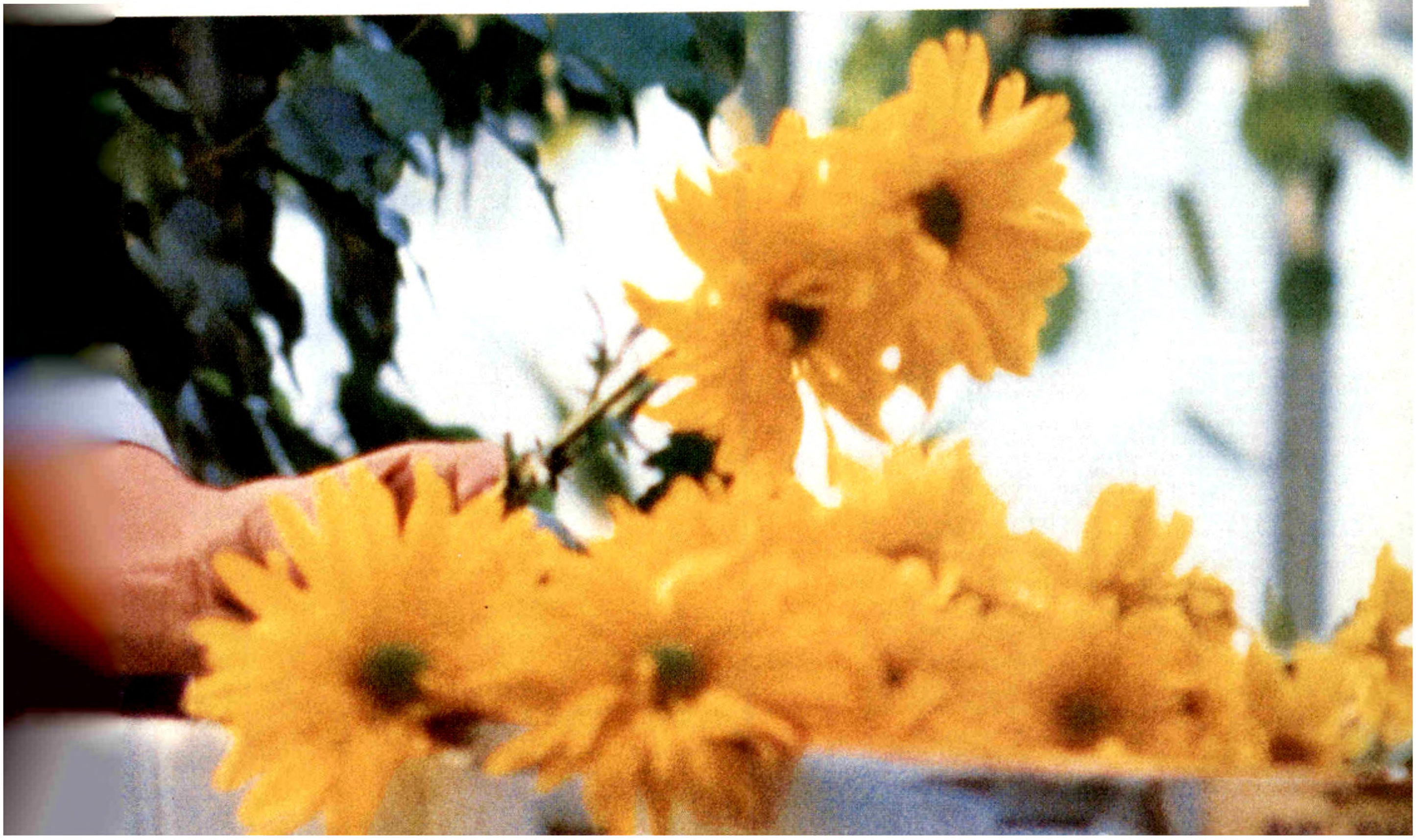

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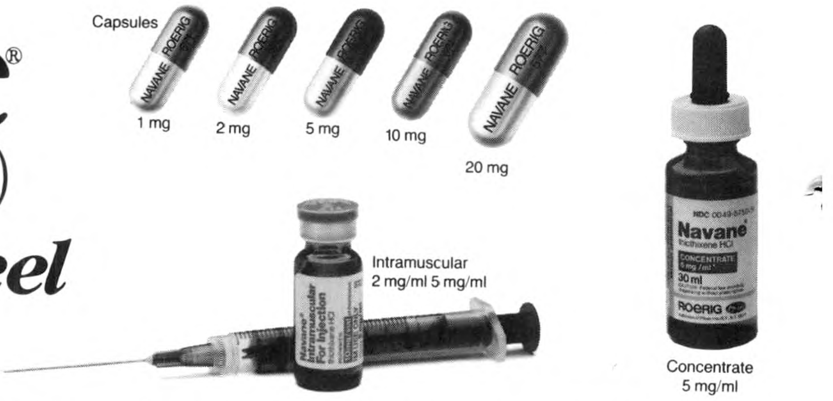

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Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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October 4–8, annual meeting, Southern Psychiatric Association, Asheville, North Carolina. Contact Margo S. Adams, Executive Secretary, P.O. Box 10002, Tallahassee, FL 32302; 904-222-8404.

October 5–7, annual meeting, National Association for Retarded Citizens, San Antonio, Texas. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue J, Arlington, TX 76006; 817-640-0204.

October 6–7, Seventh Annual Psychopharmacology Update, Boston. Contact Tufts University School of Medicine, Office of Continuing Education, Box 36, Boston, MA 02111; 617-956-6579.

October 8–11, 10th World Congress, International College of Psychosomatic Medicine, Madrid. Contact Professor J.J. Lopez-Ibor, Clinica Lopez Ibor, Calle Nueva Zelanda 44, Puerta de Hierro, E-28035 Madrid, Spain.

October 8–11, 2nd congress, World Association for Psychosocial Rehabilitation, Barcelona, Spain. Contact J.L. Marti-Tusquets, University of Barcelona, Casanova 143, Barcelona 08036, Spain.

October 10–14, 8th International Forum of Psychoanalysis, Rio de Janeiro, Brazil. Contact ADAM Congressos e Eventos Ltda., 63, Av. Almirante Barroso, Grps. 1413-1414, Rio de Janeiro 20031, R.J., Brazil; 021-220-2781.

October 11–15, annual meeting, American Academy of Child and Adolescent Psychiatry, New York. Contact Virginia Q. Anthony, Executive Director, 3615 Wisconsin Avenue, NW, Washington, DC 20016; 202-966-7300.

October 12–14, annual meeting, American Academy of Medical Administrators, Scottsdale, Arizona. Contact Thomas R. O'Donovan, Ph.D., President, 30555 Southfield Road, Suite 150, Southfield, MI 48076; 313-540-4310.

October 13–15, 6th International Conference on Multiple Personality/Dissociative States, Chicago. Contact Bennett G. Braun, M.D., Program Director, ICMP/DS, Rush-Presbyterian-St. Luke's Medical Center, 6130 North Sheridan Road, Chicago, Illinois 60660; 312-508-6440 or 508-6442.

October 13–19, 8th World Congress of Psychiatry, World Psychiatric Association, Athens, Greece. Contact Dr. Constantin R. Soldatos, Department of Psychiatry, Eginitiou Hospital, 74 Vassilissis Sophias Avenue, Athens 11528 Greece; 30 1 72 23 670.

October 14–16, annual meeting, Association of Mental Health Librarians, Philadelphia. Contact Emily Bergman, President, 2235 Beverly Boulevard, Los Angeles, CA 90057; 213-483-7034.

October 15–18, 4th International Congress on Headache, Sydney, Australia. Contact Conference Action Pty. Ltd., 88 Albany Street, Crows Nest, Sydney 2065, Australia.

October 15–20, annual meeting, American College of Surgeons, Atlanta. Contact Paul A. Ebert, M.D., Director, 55 East Erie Street, Chicago, IL 60610; 312-664-4050.

October 16–17, annual meeting, Institute of Medicine/National Academy of Sciences, Washington, DC. Contact Samuel O. Thier, M.D., President, 2101 Constitution Avenue, NW, Washington, DC 20418; 202-334-2169.

October 18–21, annual meeting, American Academy of Clinical Psychiatrists, St. Louis. Contact Alicia A. Muñoz, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-298-4782.

October 18–22, 28th World Congress on Epilepsy, New Delhi. Contact Dr. K.S. Mani, 1 Old Vety, Hospital Road, Bangalore, 560004 India.

October 19–21, "Treatment of Obesity: A Multidisciplinary Approach," sponsored by Harvard Medical School and New England Deaconess Hospital. Contact Harvard MED-CME, P.O. Box 825, Boston, MA 02117; 617-732-1528.

October 19–22, annual meeting, American Academy of Psychiatry and the Law, Washington, D.C. Contact Jonas R. Rappeport, M.D., Medical Director, 1211 Cathedral Street, Baltimore, MD 21201; 301-539-0379.

October 21–26, annual meeting, American Academy of Pediatrics, Chicago. Contact James E. Strain, M.D., Executive Director, P.O. Box 927, Elk Grove Village, IL 60009-0927; 312-288-5005.

(Continued on page A14)

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References: 1. Thompson TL II, Thompson WL. Treating depression: tricyclics, tetracyclics, and other options. *Modern Medicine.* August 1983;51:87-109. **2.** Georgotas A. Affective disorders: pharmacotherapy, In: Kaplan HI, Sadock BJ, eds. *Comprehensive Textbook of Psychiatry IV.* Baltimore, Md: Williams & Wilkins; 1985;1:821-833. **3.** Bye C, Clubley M, Peck AW. Drowsiness, impaired performance and tricyclic antidepressant drugs. *Br J Clin Pharmacol.* 1978;6:155-161. **4.** Kupfer DJ, Spiker DG, Rossi A, Coble PA, Shaw D, Ulrich R. Nortriptyline and EEG sleep in depressed patients. *Biol Psychiatry.* 1982;17:535-546. **5.** Blackwell B, Peterson GR, Kuzma RJ, Hostetler RM, Adolph AB. The effect of five tricyclic antidepressants on salivary flow and mood in healthy volunteers. *Communications in Psychopharmacol.* 1980;4:255-261. **6.** Hayes PE, Kristoff CA. Adverse reactions to five new antidepressants. *Clin Pharm.* 1986;5:471-480. **7.** Ziegler VE, Clayton PJ, Biggs JT. A comparison study of amitriptyline and nortriptyline with plasma levels. *Arch Gen Psychiatry.* May 1977;34:607-612.

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The concomitant administration of quinidine and nortriptyline may result in a significantly longer plasma half-life, higher A.U.C. and lower clearance of nortriptyline.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania; exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

[PAM-Z17—1/13/89]

Dorsey Division
SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

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PAM-289-13R

(Continued from page A12)

October 22–27, 24th World Congress on Neurology, New Delhi. Contact Dr. J.S. Chopra, Organizing Secretary, 1033 Sector 24 B, Chandigarh 160 023, India.

October 22–27, annual meeting, American Health Care Association, New Orleans. Contact Paul R. Willging, Ph.D., Executive Vice-President, 1200 15th Street, N.W., 8th Floor, Washington, DC 20005-2899; 202-833-2050.

October 25–26, Autumn Quarterly Meeting of the Royal College of Psychiatrists, London. Contact Royal College of Psychiatrists, 17 Belgrave Square, London SW1X 8PG, United Kingdom; 44-1-235-2351.

October 25–28, Midwest Addictions Conference, 1989, "Forward to the Fundamentals: Chemical Dependency and Psychiatry," Detroit. Contact Diane Campbell, Samaritan Health Center, 5555 Conner Avenue, Detroit, MI 48213; 313-579-4000.

October 25–29, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, San Francisco. Contact John A. Hinckley, Executive Director, P.O. Box 11086, Richmond, VA 23230; 804-355-0147.

October 26–28, annual meeting, Milton H. Erickson Foundation, Inc., Phoenix. Contact Jeffrey K. Zeig, Ph.D., 3606 North 24th Street, Phoenix, AZ 85016; 602-956-6196.

October 26–29, 47th annual conference, American Association for Marriage and Family Therapy, San Francisco. Contact AAMFT, Department C, 1717 K Street, NW, #407, Washington, DC 20006; 202-429-1825.

October 26–29, annual meeting, Academy of Psychosomatic Medicine, Las Vegas. Contact Evelyne Hallberg, Executive Director, 5824 N. Magnolia, Chicago, IL 60660; 312-784-2025.

October 28–November 2, annual meeting, Association of American Medical Colleges, Washington, DC. Contact Robert G. Petersdorf, M.D., President, One Dupont Circle, N.W., Suite 200, Washington, DC 20036; 202-828-0400.

October 29–November 3, annual meeting, Society for Neuroscience, Phoenix, Arizona. Contact Nancy Beang, Executive Director, 11 Dupont Circle, N.W., Suite 500, Washington, DC 20036; 202-462-6688.

NOVEMBER

November 3–5, special conference, "Freud: Impact onTwentieth Century Thought," Columbia, South Carolina. Contact Gerry Herron, Division of Psychoanalysis, Department of Neuropsychiatry and Behavioral Science, University of South Carolina, School of Medicine, Columbia, SC 29208; 803-734-7432.

November 5–7, 6th annual conference, The Chronic Patient: Care and Treatment, "The Family: A Crucial Link to Recovery," Jacksonville, Florida. Contact Ed R. Paat, M.S., University Hospital, Community Mental Health Center, 655 West 8th Street, Jacksonville, FL 32209; 904-350-6806.

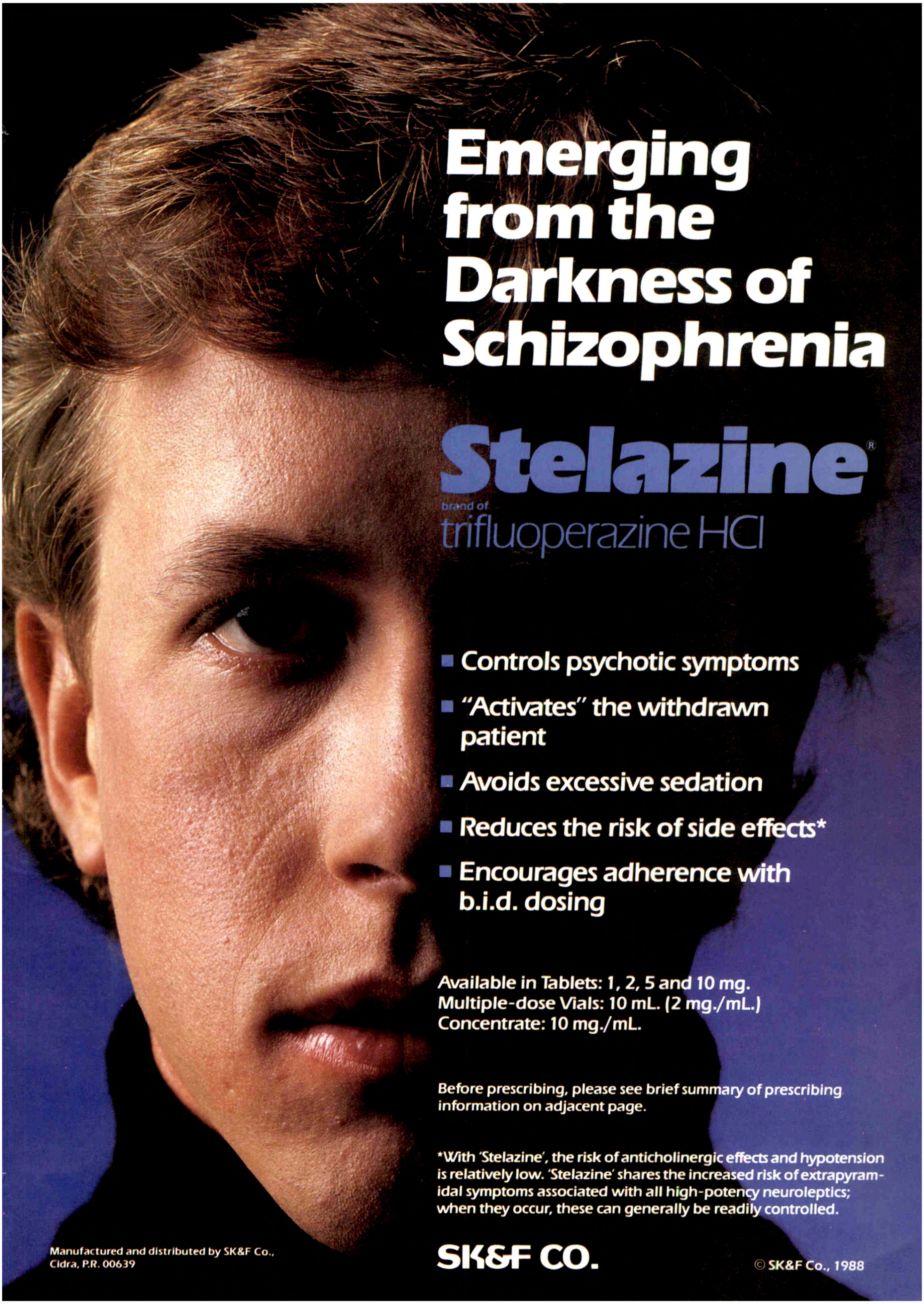
November 10, special conference, Mount Sinai Hospital, Academic Day VIII presents "Group Psychotherapy for the 1990's," Toronto. Contact M. Leszcz, M.D., F.R.C.P., Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5; 416-586-4567.

November 10–11, special conference, "Suicide Risk in the Elderly: Clinical Assessment and Management," Boston Society for Gerontologic Psychiatry, Boston. Contact Sandra White, 64 Hancock Avenue, Newton, MA 02159; 617-527-5550.

November 10–12, 2nd annual U.S. Psychiatric and Mental Health Congress, New York. Contact Andrea Crossetta, Conference Management Corporation, 200 Connecticut Avenue, Norwalk, CT 06856-4990; 203-852-0500, ext. 226.

November 13–17, International Conference on Rehabilitation Psychiatry, Arusha, Tanzania. Contact Dr. G.P. Kilonzo, Head, Department of Psychiatry, Muhimbili Medical Centre, P.O. Box 65293, Dar Es Salaam, Tanzania.

November 30–December 3, Fall Symposium of the American Back Society, Las Vegas. Contact the American Back Society, 2647 East 14th Street, Suite 401, Oakland, CA 94601; 415-536-9929.



Emerging from the Darkness of Schizophrenia

Stelazine®

brand of
trifluoperazine HCl

- Controls psychotic symptoms
- "Activates" the withdrawn patient
- Avoids excessive sedation
- Reduces the risk of side effects*
- Encourages adherence with b.i.d. dosing

Available in Tablets: 1, 2, 5 and 10 mg.
Multiple-dose Vials: 10 mL. (2 mg./mL.)
Concentrate: 10 mg./mL.

Before prescribing, please see brief summary of prescribing information on adjacent page.

*With 'Stelazine', the risk of anticholinergic effects and hypotension is relatively low. 'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics; when they occur, these can generally be readily controlled.

Manufactured and distributed by SK&F Co.,
Cidra, P.R. 00639

SK&F CO.

© SK&F Co., 1988

Stelazine® brand of
trifluoperazine HCl

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

SK&F CO.
Manufactured and distributed by
SK&F Co., Cidra, P.R. 00639

BRS-SZ:L63

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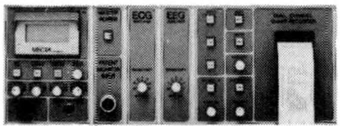
INTELLIGENT ECT FROM MECTA CORP.
UL LISTED CSA CERTIFIED
MODULAR AND COMPUTERIZED

SR-1

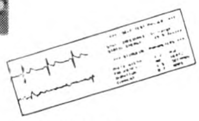


JR-1

FLEXIBILITY

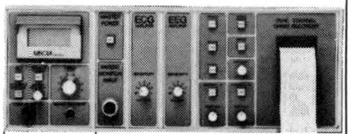
SR/JR FEATURES INCLUDE:

- Continuous reading of energy in Joules
- Tiltable Liquid Crystal Display
- Bi-polar brief pulse stimulus
- Adjustable constant current stimulus
- Audible warning prior to treatment
- Remote control capabilities
- 100% expected seizure induction
- Totally isolated for maximum safety
- Single or multiple energy control(s)
- All parameters displayed in text form
- Increased energy for difficult cases
- Built-in self test for patient safety
- Steady warning tone during treatment
- Protected STIMULUS CONTROL push button
- Timing accuracy better than .1%
- 1 year parts and labor warranty
- Operates on 120 or 240 VAC
- Complete with all accessories



PRINTED SELF TEST AND TREATMENT RESULTS

SR-2



JR-2

ADDITIONAL FEATURES INCLUDED WITH ALL SR MODELS ARE:

- EEG instrumentation amplifier
- Built-in 2 channel digital chart recorder
- Numeric timing marks during monitoring
- Printed record of energy level
- Printed date and time of treatment
- ECG instrumentation amplifier
- Selectable single or dual channel
- Printed record of treatment and self test
- Printed record of stimulus parameters
- Modular design for maximum flexibility

SINGLE ENERGY LEVEL CONTROLS

SIMPLICITY

MECTA Corporation 5622 SW Kelly Street Portland, OR 97201 (503) 245-6975

FOUNDATIONS' FUND PRIZE FOR RESEARCH IN PSYCHIAIRY

The American Psychiatric Association takes pleasure in inviting submissions for the thirteenth annual foundations' fund prize for research in psychiatry.

Candidates for this prize should be citizens of the United States or Canada and should be nominated by a sponsor. Sponsors should be members of the American Psychiatric Association. Members of the prize board are excluded from submitting nominations.

The *Sponsor* should submit

A supporting letter (six copies) setting out in detail justification for the nomination and summarizing the research accomplishments of the nominee in a specific area or with a coherent theme.

The *Nominee* should submit

(A) A book or paper (six copies), or a group of representative, and thematically linked, books or papers (six copies) published in English (or accepted for publication) and dated within ten years prior to the deadline of submission.

(B) A summary statement (six copies) written by the nominee, emphasizing the Principal Theme *running through the work, its internal cohesiveness and consistency, and scientific implications.*

(C) An up-to-date curriculum vitae (six copies)

(D) An up-to-date bibliography (six copies)

All entries must be submitted in *six complete collated sets* and sent to Ira D. Glick, M.D., Chairman, Foundations' Fund Prize Board for Research in Psychiatry, American Psychiatric Association, 1400 K Street, N.W., Washington, D.C. 20005. Entries will be acknowledged, but cannot be returned. The prize is based on a yearly competition. Resubmission is permitted. The award will be presented at the Convocation of Fellows at the Association's Annual Meeting in May of 1990.

The deadline for submission is *November 1, 1989*.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

NEW Wellbutrin®
(BUPROPION HCl)

helps clear depression with few life-style disruptions.

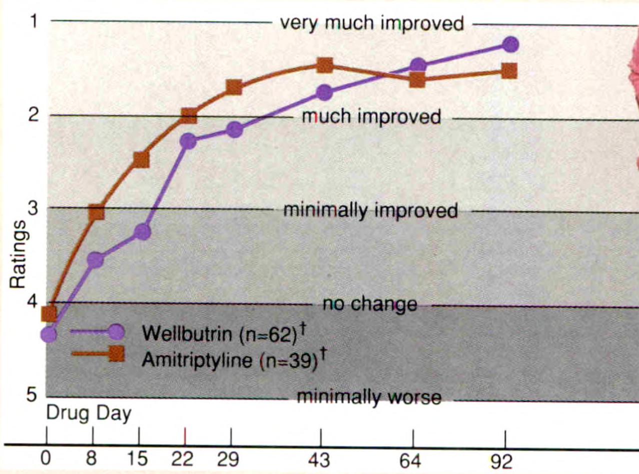
See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

Chemically unique WELLBUTRIN is unrelated to tricyclics/tetracyclics, monoamine oxidase inhibitors, or other known antidepressants.

WELLBUTRIN relieves depression as effectively as amitriptyline.

Clinical Global Improvement*



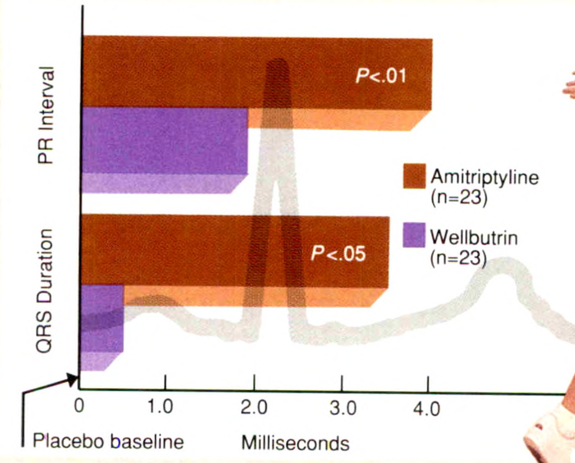
* Adapted from Mendels et al.[1]

†Dosages were 300 to 450 mg/day for WELLBUTRIN, 75 to 150 mg/day for amitriptyline.

Please review IMPORTANT CONSIDERATIONS BEFORE PRESCRIBING WELLBUTRIN on page 6 and brief summary on the last pages of this advertisement before prescribing WELLBUTRIN.

WELLBUTRIN relieves depression with no clinically significant effect on cardiac conduction.

Average Change in EKG Parameters from Baseline Values During Treatment*



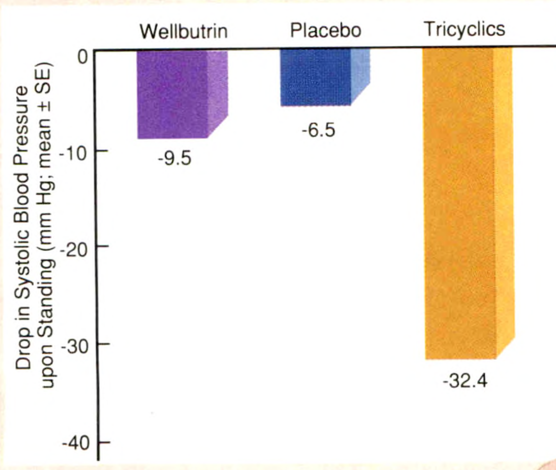
* Adapted from Wenger et al.[2]

> *"By contrast, the present results with bupropion support the* in vitro *data demonstrating that this antidepressant lacks these undesirable electro-physiologic properties, and imply that bupropion has a substantially wider margin of safety in man than amitriptyline with regard to cardiac conduction."*[2]

Feeling better
Living better

WELLBUTRIN relieves depression with no clinically significant orthostatic hypotension.

Orthostatic Blood Pressure Change (mm Hg)*



* Adapted from Farid et al.[3]

NEW Wellbutrin®
(BUPROPION HCl)

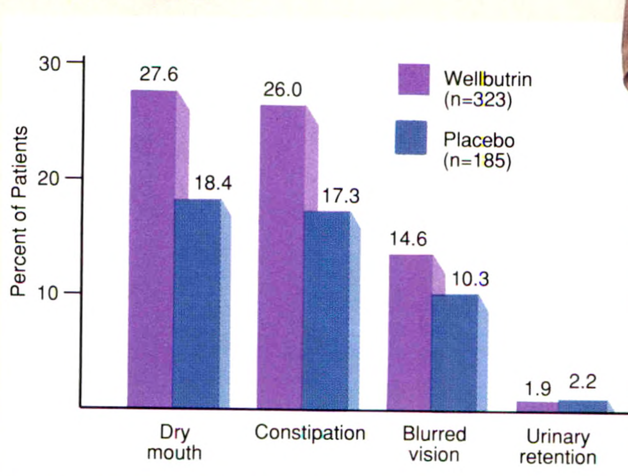
Helping patients to feel better and live better.

See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

WELLBUTRIN relieves depression with few anticholinergic side effects.

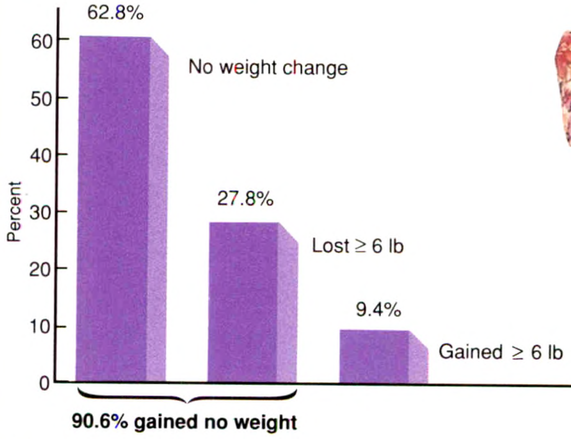
Percent Difference in Anticholinergic Effects Relative to Placebo*



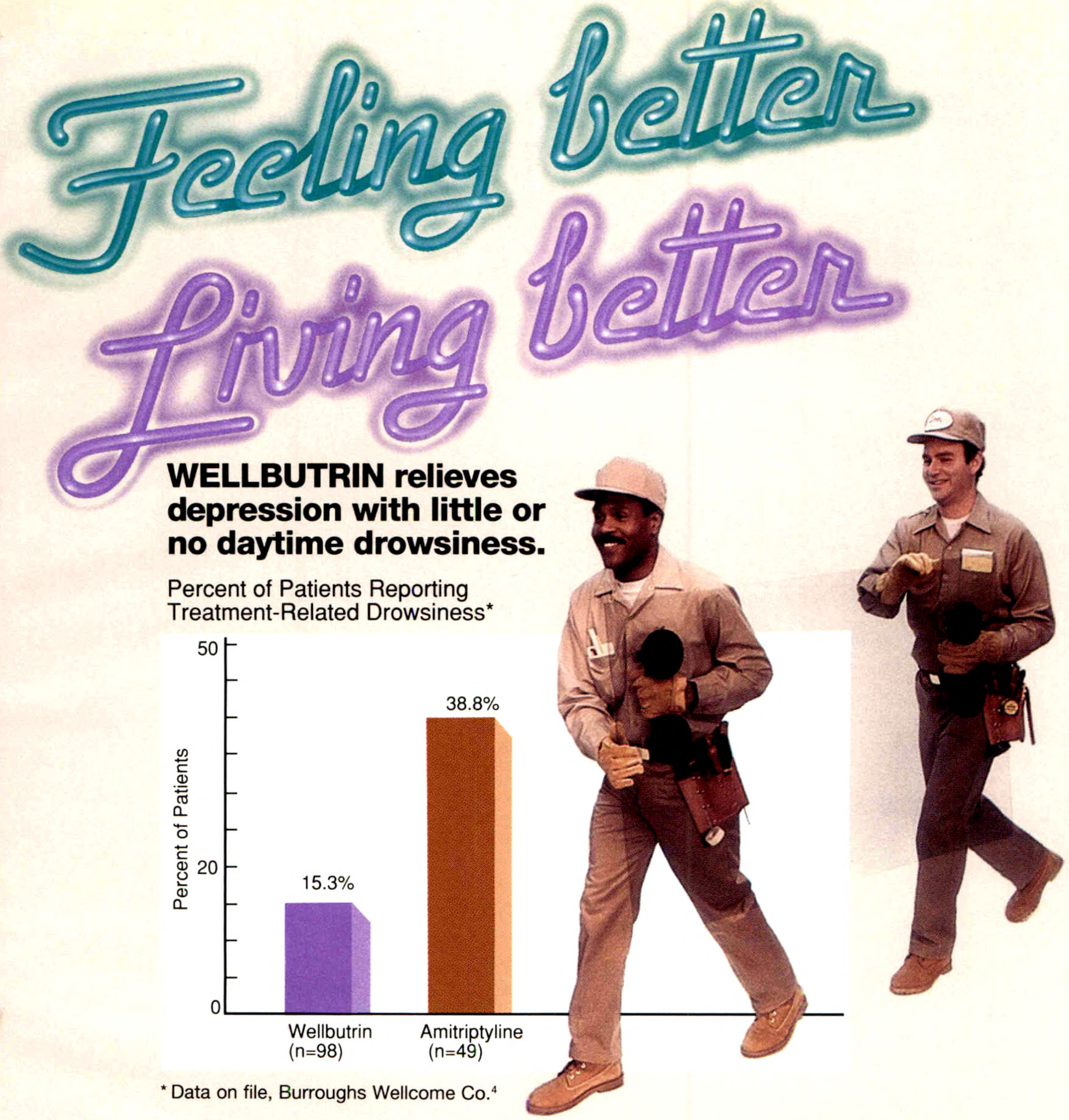
* Data on file, Burroughs Wellcome Co.[4]

WELLBUTRIN relieves depression with little or no weight gain.

Change in Body Weight (percent of patients; n=341)*



* Data on file, Burroughs Wellcome Co.[4]



WELLBUTRIN relieves depression with little or no daytime drowsiness.

Percent of Patients Reporting Treatment-Related Drowsiness*

* Data on file, Burroughs Wellcome Co.[4]

In placebo-controlled clinical trials, the incidence of drowsiness* for patients treated with WELLBUTRIN was 19.8%, versus 19.5% for those receiving placebo.

Agitation and Insomnia: A substantial proportion of patients treated with WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of WELLBUTRIN treatment.

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**As with all drugs in this category, patients should be cautioned that the ability to perform tasks requiring judgment or motor and cognitive skills may be impaired.*

NEW Wellbutrin®

(BUPROPION HCl)

Helping patients to feel better and live better.

See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

Feeling better
Living better

Wellbutrin® (bupropion HCl)
helps clear depression with few life-style disruptions.

Important considerations before prescribing Wellbutrin.

Patient Selection Criteria
WELLBUTRIN is contraindicated in patients

- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa
- on monoamine oxidase (MAO) inhibitor therapy
- who are allergic to it

(See CONTRAINDICATIONS section of full prescribing information.)

WELLBUTRIN should be administered with extreme caution to patients

- with a history of seizure, cranial trauma, or other factors that predispose toward seizure
- taking other agents or other treatment regimens that may lower seizure threshold

(See WARNINGS section of full prescribing information.)

Overdosage
In 13 cases of overdose involving WELLBUTRIN, there were no deaths or lasting sequelae.

Seizures
A wide range of seizure rates have been reported with antidepressant therapy with some reports as low as 0.1%. The incidence of seizures with WELLBUTRIN is approximately 0.4%, which may be as much as fourfold higher than some other antidepressants, although no direct comparative studies have been conducted.

Dosage and Administration
The recommended starting dose of WELLBUTRIN is 200 mg/day given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day given as 100 mg t.i.d. no sooner than three days after beginning therapy.

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1-3	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Increases in dose should not exceed 100 mg/day in a three-day period. WELLBUTRIN is available in both 75 mg and 100 mg tablets.

Important: No single dose of WELLBUTRIN should exceed 150 mg because a higher incidence of seizures has been observed in patients receiving higher individual doses of WELLBUTRIN. For this reason, too, patients should be reminded that they should not double up on any dose because they missed a previous one. Dosage should not exceed 450 mg per day (see WARNINGS).

Clinical trials involving more than 7,000 depressed patients and over 200 investigators demonstrated that **WELLBUTRIN relieves depression in a wide range of patients:**

- with no clinically significant effects on cardiac conduction
- with no clinically significant orthostatic hypotension
- with few anticholinergic side effects
- with little or no weight gain
- with little or no daytime drowsiness

NEW Wellbutrin
(BUPROPION HCl)

See brief summary of full prescribing information on last pages of this advertisement.

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

CONTRAINDICATIONS: Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

WARNINGS:

SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the pre-approval evaluation period, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

***Recommendations for reducing the risk of seizure:* Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS:

General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Wellbutrin was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients:

Patients should be instructed to take Wellbutrin in equally divided doses three or four times a day to minimize the risk of seizure.

Patients should be told that any CNS-active drug like Wellbutrin may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin does not adversely affect their performance they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of coadministered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's pre-approval clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	18.9
Weight Gain	13.6	22.7
Weight Loss	23.2	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbance	5.3	3.2
Blurred Vision	14.6	10.3
Gustatory Disturbance	3.1	1.1

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the entire pre-approval evaluation of Wellbutrin: During its pre-approval assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare was lymphadenopathy.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epistaxis and rate or rhythm disorder.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were body odor, surgically related pain, infection, medication reaction and overdose.

Post-Approval Reports: The following additional events were rarely observed (less than 1/1000 patients) post-approval.

Cardiovascular: Flushing and myocardial infarction.

Dermatologic: Acne.

Gastrointestinal: Stomach ulcer.

Hematologic/Oncologic: Anemia and pancytopenia.

Neurological: Aphasia.

Musculoskeletal: Musculoskeletal chest pain.

Respiratory: Pneumonia and pulmonary embolism.

OVERDOSAGE:

Human overdose experience: There has been limited clinical experience with overdosage of Wellbutrin. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of Wellbutrin and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer Wellbutrin in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose should not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d., preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing should begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day, given as 100 mg t.i.d., no sooner than 3 days after beginning therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full antidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longer. An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.d. with at least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate an adequate response after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly and to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of antidepressant drugs.

References: 1. Mendels J, Amin MM, Chouinard G, et al. A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychiatry.* 1983;44(5, sec 2):118-120. **2.** Wenger TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion and amitriptyline on cardiac conduction in depressed patients. *J Clin Psychiatry*. 1983;44(5, sec 2):174-175. **3.** Farid FF, Wenger TL, Tsai SY, et al. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. *J Clin Psychiatry.* 1983;44 (5, sec 2):170-173. **4.** Data on file, Burroughs Wellcome Co.

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The Less Sedating Therapy for Tourette Syndrome

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* ORAP is indicated for patients who have failed to respond satisfactorily to standard treatment.

Please see following page for a brief summary of prescribing information.

ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS–Information for Patients).

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS–Information for Patients.)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS–Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 60 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery This drug has no recognized use in labor or delivery.

Nursing Mothers It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General: Extrapyramidal Reactions Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs. Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia: Hyperpyrexia has been reported with other antipsychotic drugs.

Clinical Trials The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Senses		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema

Cardiovascular/Respiratory: Postural hypotension, hypotension, hypertension, tachycardia, palpitations

Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress

Endocrine: Loss of libido

Metabolic/Nutritional: Weight gain, weight loss

Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia

Psychiatric: Excitement

Skin: Rash, sweating, skin irritation

Special Senses: Blurred vision, cataracts

Urogenital: Nocturia, urinary frequency

Postmarketing Reports The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS–Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP 2"–NDC 0093-0187-01, bottles of 100.

Dispense in tight, light-resistant containers as defined in the official compendium.

Made in Canada

Manufactured by:
McNeil Pharmaceutical, (Canada) Ltd.
Stouffville, Ontario L4A 7X7

Printed in USA
Rev. A 6/88

Manufactured for:
LEMMON COMPANY
Sellersville, PA 18960

LEMMON

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1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

TRUST 35 YEARS OF PROVEN EXPERIENCE

THORAZINE®

brand of chlorpromazine

See adjacent page for brief summary of prescribing information.

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THORAZINE®
brand of
# chlorpromazine

See complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Comatose states or presence of large amounts of C.N.S. depressants.

Warnings: The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

Precautions: Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce α-adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin®* metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Amipaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Amipaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

Adverse Reactions: Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

How Supplied: Tablets: 10 mg., 25 mg. or 50 mg., in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 100 mg. and 200 mg., in bottles of 100 and 1000; in Single Unit Packages of 100 (intended for institutional use only).

Spansule® brand of sustained release capsules: 30 mg., 75 mg., 150 mg. or 200 mg., in bottles of 50 and 500; in Single Unit Packages of 100 (intended for institutional use only). For use in severe neuropsychiatric conditions, 300 mg., in bottles of 50; in Single Unit Packages of 100 (intended for institutional use only).

Ampuls: 1 mL. and 2 mL. (25 mg./mL.), in boxes of 10, 100 and 500.

Multiple-dose Vials: 10 mL. (25 mg./mL.), in boxes of 1, 20 and 100.

Syrup: 10 mg./5 mL. in 4 fl. oz. bottles.

Suppositories: 25 mg. or 100 mg., in boxes of 12.

Concentrate: 30 mg./mL., in 4 fl. oz. bottles and in cartons of 36 bottles. 100 mg./mL., in 8 fl. oz. bottles, in cartons of 12.

*phenytoin, Parke-Davis.
†metrizamide, Winthrop Pharmaceuticals.

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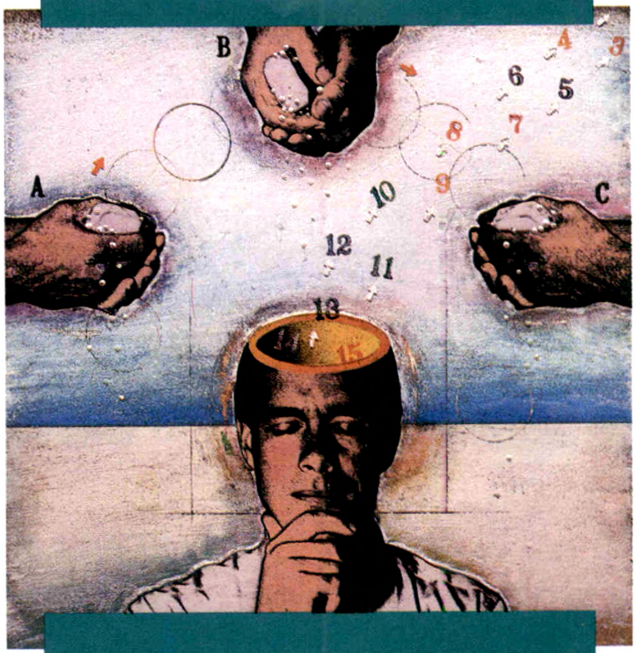

A treatment IND (investigational new drug) program for patients with Obsessive-Compulsive Disorder

FDA procedures now bring promising investigational drugs to patients earlier in the development process.

The Food and Drug Administration has established procedures to allow use of "...promising drugs for treatment of patients with serious or life-threatening illnesses..."[1] as early in the drug development process as possible and before general marketing has begun.

This OCD medication is the first psychotropic drug authorized under these new procedures.

In releasing the drug for treatment use, the FDA explained that "...studies aimed at U.S. approval... have shown sufficient evidence of effectiveness for the drug to permit its limited distribution."[2]

Ready supply of drug available through enrolled psychiatrists for eligible patients.

The treatment medication is being distributed by CIBA-GEIGY free of charge to psychiatrists enrolled in the treatment IND program, who will, in turn, supply the drug to eligible patients.

Patient enrollment criteria established.

Patients must be between 10 and 70 years of age, with OCD symptoms of at least one year's duration that interfere significantly with daily functioning.

For information and enrollment kits call
1-800-842-2422
between 9AM-5PM Eastern Time

---

[1] Young FE, Benson JS, Nightingale SL, et al: Drugs available under treatment IND. *FDA Drug Bulletin* 1988:18:14-15.
[2] FDA Press Release, June 6, 1988.

P24,368.

Announced by
CIBA–GEIGY
Pharmaceuticals
Summit, New Jersey 07901

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Books Received

The Social Psychology of Work, 2nd ed., by Michael Argyle. New York, Penguin Books, 1989, 380 pp., $8.95 (paper).

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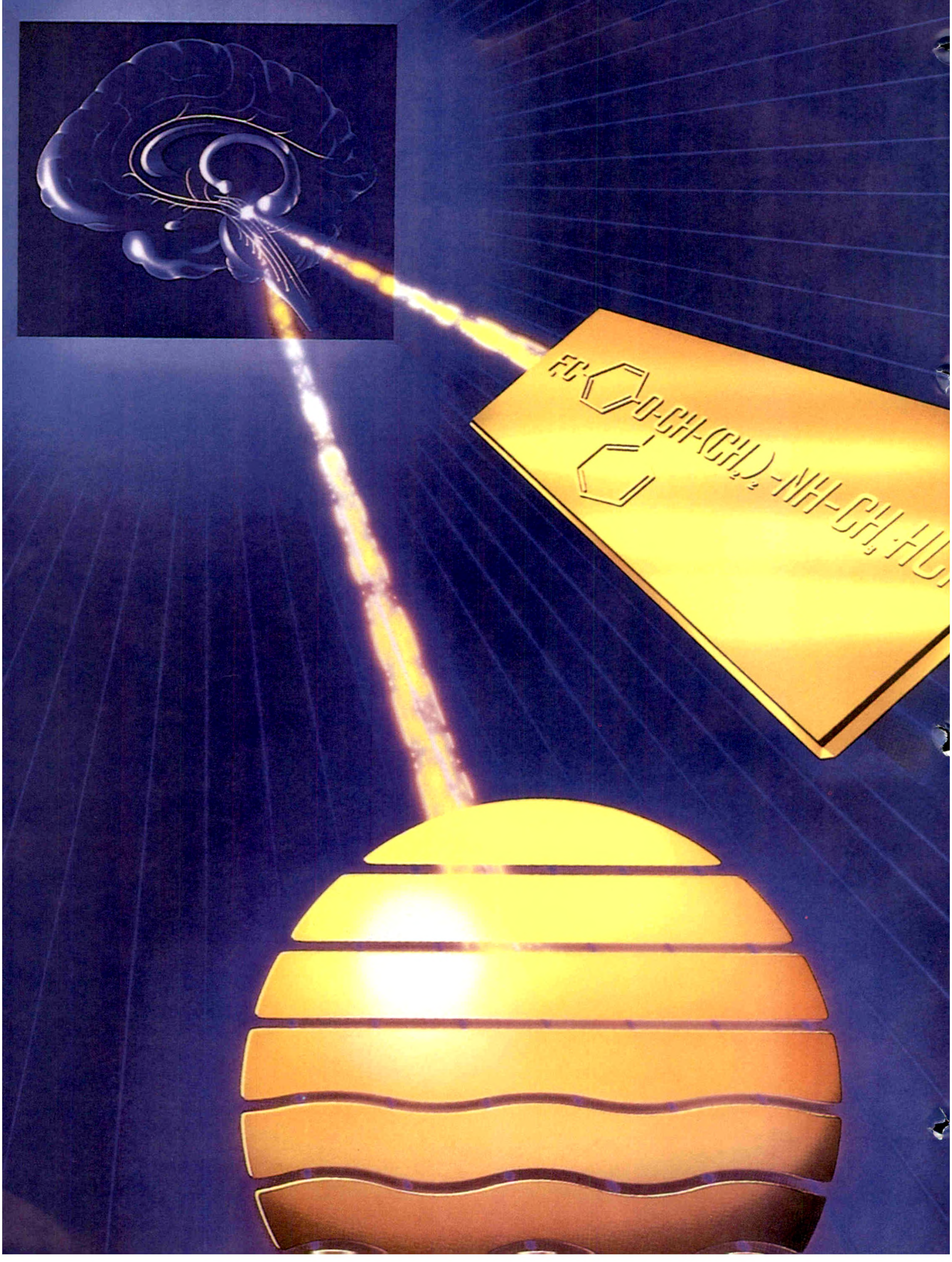
The synapse—crossroads for serotonin



In depression

PROZAC®

fluoxetine hydrochloride

"a potent serotonin reuptake inhibitor... represents a new class of antidepressants."[1]

Effectively relieves depression*

Unlike the tricyclics, Prozac specifically inhibits serotonin uptake. Its minimal action on other neurotransmitters may explain its favorable side-effect profile.

Fewer side effects to disrupt therapy

Side effects are generally mild and manageable, and include nausea, anxiety/nervousness, insomnia, and drowsiness

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Avoid using MAO inhibitors concomitantly or in proximity to Prozac

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Rash and/or urticaria occurred in 4% of clinical trial patients

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A wide margin of safety

20-mg once-a-day therapy

PROZAC...
A *specifically* different antidepressant

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1. *Curr Ther Res* 1986;39:559–563.
*As defined by DSM-III.

See adjacent page for brief summary of prescribing information.

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Prozac®

fluoxetine hydrochloride

Brief Summary: Consult the package literature for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindication: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: *Monoamine Oxidase Inhibitors* — Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events — During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General* — Anxiety and Insomnia — Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight — Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania — During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures — Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide — The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites — Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* Clinical Pharmacology *and* Dosage and Administration).

Use in Patients With Concomitant Illness — Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients — Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests — There are no specific laboratory tests recommended.

Drug Interactions — As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Tryptophan — Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors — *See* Warnings.

Other Antidepressants — There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Diazepam Clearance — The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins — Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

CNS-Active Drugs — The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Electroconvulsive Therapy — There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility — There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy — Teratogenic Effects — Pregnancy Category B — Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery — The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers — It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children — Safety and effectiveness in children have not been established

Usage in the Elderly — Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hyponatremia — Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: *Commonly Observed* — The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment — Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event			Percentage of Patients Reporting Event	
Body System/ Adverse Event*	Prozac (N=1,730)	Placebo (N=799)	Body System/ Adverse Event*	Prozac (N=1,730)	Placebo (N=799)
Nervous			**Body as a Whole**		
Headache	20.3	16.5	Asthenia	4.4	1.9
Nervousness	14.9	8.5	Infection, viral	3.4	3.1
Insomnia	13.8	7.1	Pain, limb	1.6	1.1
Drowsiness	11.6	6.3	Fever	1.4	—
Anxiety	9.4	5.5	Pain, chest	1.3	1.1
Tremor	7.9	2.4	Allergy	1.2	1.1
Dizziness	5.7	3.3	Influenza	1.2	1.5
Fatigue	4.2	1.1	**Respiratory**		
Sedated	1.9	1.3	Upper respiratory infection	7.6	6.0
Sensation disturbance	1.7	2.0	Flu-like syndrome	2.8	1.9
Libido, decreased	1.6	—	Pharyngitis	2.7	1.3
Light-headedness	1.6	—	Nasal congestion	2.6	2.3
Concentration, decreased	1.5	—	Headache, sinus	2.3	1.8
Digestive			Sinusitis	2.1	2.0
Nausea	21.1	10.1	Cough	1.6	1.6
Diarrhea	12.3	7.0	Dyspnea	1.4	—
Mouth dryness	9.5	6.0	**Cardiovascular**		
Anorexia	8.7	1.5	Hot flushes	1.8	1.0
Dyspepsia	6.4	4.3	Palpitations	1.3	1.4
Constipation	4.5	3.3	**Musculoskeletal**		
Pain, abdominal	3.4	2.9	Pain, back	2.0	2.4
Vomiting	2.4	1.3	Pain, joint	1.2	1.1
Taste change	1.8	—	Pain, muscle	1.2	1.0
Flatulence	1.6	1.1	**Urogenital**		
Gastroenteritis	1.0	1.4	Menstruation, painful	1.9	1.4
Skin and Appendages			Sexual dysfunction	1.9	—
Sweating, excessive	8.4	3.8	Frequent micturition	1.6	—
Rash	2.7	1.8	Urinary tract infection	1.2	—
Pruritus	2.4	1.4	**Special Senses**		
			Vision disturbance	2.8	1.8

---

*Events reported by at least 1% of Prozac-treated patients are included.
— Incidence less than 1%.

Incidence in Controlled Clinical Trials — Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac — During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole — *Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System — *Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System — *Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System — *Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional — *Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System — *Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System — *Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses — *Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System — *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports — Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, and thrombocytopenia.

Overdosage: *Human Experience* — As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (*see* Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

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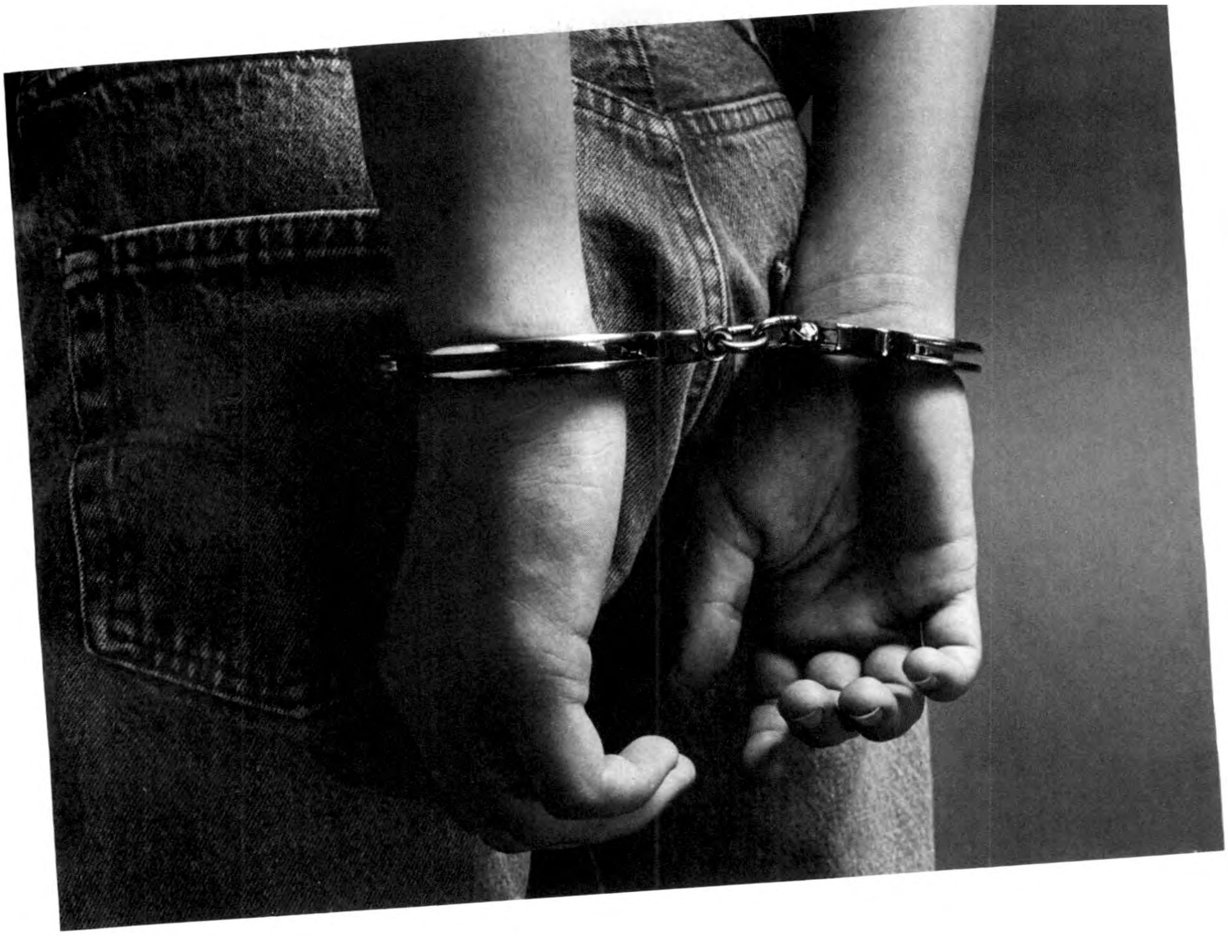

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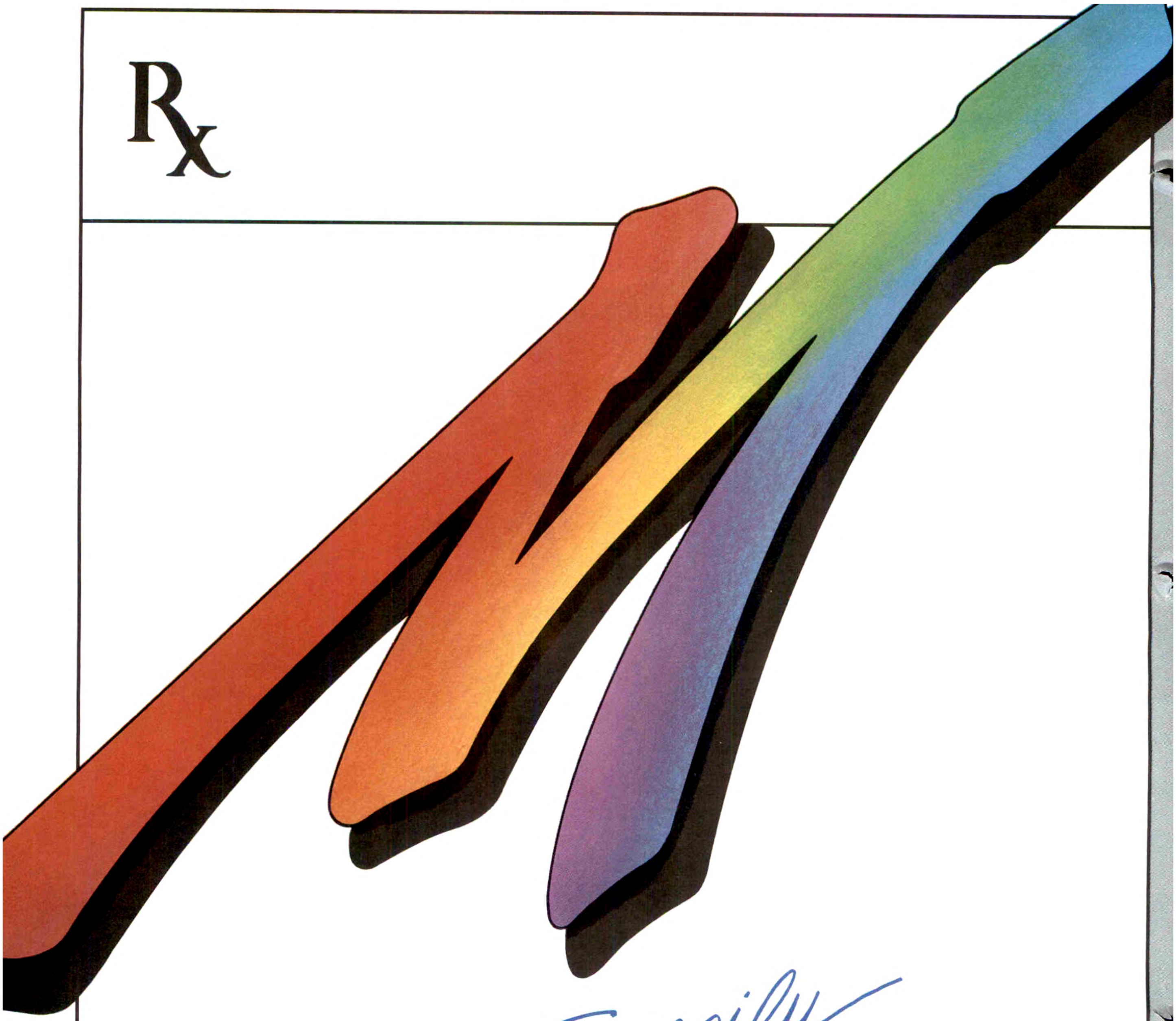

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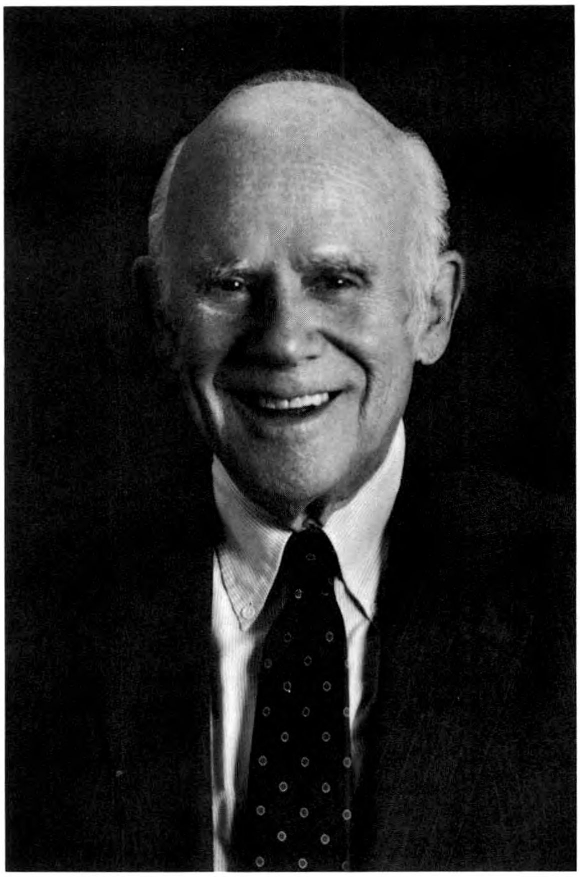

Morris A. Lipton, Ph.D., M.D.
1915–1989

On Thursday, March 23, 1989, a Memorial Service was held for Dr. Morris A. Lipton in the Clinic Auditorium of the University of North Carolina School of Medicine in Chapel Hill. His death a week earlier had not been unexpected, for he had developed a serious illness some months before, despite which he had maintained a full schedule of professional activities almost to the end. And when the end came, he was at home in the midst of his family and surrounded by the friends and colleagues with whom he had lived and worked for so many years.

One might almost say that even in his death Morrie was as much at the center of things as he had always been during his long and productive life. The Memorial Service itself was a case in point. Sitting in a teaching auditorium in familiar clinical surroundings, one might well have been attending weekly grand rounds—an illusion made all the more real by an audience sprinkled with white-coated men and women and by the inevitable, strident beeper that intermittently summoned one or another of them to slip silently out with exaggerated unobtrusiveness. It was a setting that Morrie knew well, and he was there as he had been so many scores of times before—except that now he was not a participant in the proceedings but was himself the subject of the speakers who followed one another to the podium.

Each of these spoke of that aspect of Morrie's life that each knew best, and in the aggregate they superimposed the lineaments of a deeply human portrait on a curriculum vitae that, however impressive as a list of accomplishments, was by itself little more than a dry chronicle of events. Colleagues praised the acuteness of his scientific observation, the fertile inventiveness of his mind, and his skill as an administrator that had helped him to lead an academic department of psychiatry to a position of eminence in teaching and research. And they admired him, too, for his lively social conscience and his devoted public service as an active member of committees and organizations dedicated to furthering human rights, human dignity, and human freedom. Former students, now national leaders in their own right, paid living tribute to Morrie's importance as a teacher. Family members attested to his consistently vital presence at home as a husband and father, always available and caring, no matter how demanding his professional responsibilities. All who had lived with him, worked with him, played with him, spoke of Morrie with deep affection—such was the power of his own warmth and humor to bind others to him in enduring relationships.

For those of us on the *Journal* Editorial Staff who attended the Memorial Service, it was a useful and revealing experience to listen to the speakers, for their remarks put our own more limited association with Morrie into a broader perspective. We had, of course, always known in the abstract, so to speak, of his remarkable scientific and academic accomplishments, but here we saw them come alive as they had affected and were reflected in the minds and hearts of his family and lifelong colleagues. And, as we heard them talk, we saw that in our own more restricted relationship within the context of the *Journal*, we, too, had known the same Morris Lipton whom his colleagues had known and loved in the wider professional world. Indeed, the same personal virtues and characteristics they praised had been eminently visible in his performance as Deputy Editor of the *Journal* during the last eight years of his life. Asked to join the *Journal* Editorial Board in that capacity because of his profound knowledge of the biological aspects of psychiatric illness, Morrie threw himself with enthusiasm into all aspects of the *Journal*'s operations. He was incisively critical in his editorial judgments, and in his reading of manuscripts he was as responsive to new and original ideas as he was impatient with old nonsense. He was particularly helpful and supportive with authors who had something important to say and did not quite know how to say it; with these he was a sedulous editorial midwife, remaining in attendance until they had finally brought forth a publishable paper. Under his ministrations, individual authors, and the *Journal* as well, increased in scientific stature.

But perhaps most of all we shall miss the companionship we shared with Morrie during our regular visits together to the *Journal*'s Washington office. In *obiter dicta* that punctuated the long hours of reviewing manuscripts and during relaxed conversations at dinner after the day's work was done, we ranged far and wide together over topics both personal and professional and found therein much of mutual concern, interest, and pleasure. What began as collegiality became an abiding friendship; we part company now only because we must. *Stet amicitia.*

J.C.N.

THE AMERICAN JOURNAL OF PSYCHIATRY

Psychotic Disorders in *DSM-III-R*

Kenneth S. Kendler, M.D., Robert L. Spitzer, M.D., and Janet B.W. Williams, D.S.W.

The authors review the important changes in the three sections of DSM-III-R *that include only psychotic disorders (schizophrenia, delusional disorder, and psychotic disorders not elsewhere classified), outline the rationale for these changes, and, where available, review their empirical basis. In addition, they review two proposed changes that were not incorporated into* DSM-III-R. *They conclude by calling for an increasingly rigorous and data-based process of nosologic revision.*

(Am J Psychiatry 1989; 146:953–962)

The three sections in our current nomenclature that contain only psychotic disorders (schizophrenia, delusional disorder, and psychotic disorders not elsewhere classified) underwent a number of changes from *DSM-III* to *DSM-III-R*. The purpose of this essay is to review all of the major and several of the more minor changes introduced in these sections in *DSM-III-R*, to outline their rationale, and to review, where available, their empirical basis. We also review two proposed changes in these sections which were not incorporated into *DSM-III-R*. Because it is not practical to reproduce all of the relevant criteria here, readers may find this paper easier to follow if they refer, when appropriate, to criteria in *DSM-III* and *DSM-III-R*.

The APA Advisory Committee on Psychotic Disorders for the Revision of *DSM-III* was composed of 13 individuals (see acknowledgment). This report represents *the authors'* understanding of the rationale for the changes introduced in this section in *DSM-III-R*. Not all committee members may agree with the views expressed here. In this article we will emphasize the empirical evidence available to those working on *DSM-III-R*, and not studies that may have been completed since that time.

SCHIZOPHRENIA

The Characteristic Psychotic Symptoms or Criterion A

Five noteworthy changes were made in this criterion in *DSM-III-R*. First, since a common complaint about criterion A for schizophrenia in *DSM-III* was its complexity, in *DSM-III-R* criterion A was reduced from six to three items, with item 1 now a compound item requiring two of a list of five possible symptoms or signs. For example, the two *DSM-III* items for auditory hallucinations (A-4 and A-5) were collapsed into a single *DSM-III-R* item (A-3). The intent of these changes in criterion A was to simplify with minimal content change. Second, changes in the criteria for delusional (paranoid) disorder required the elimination of criterion A-2 in *DSM-III* (somatic, grandiose, religious, nihilistic, or other delusions without persecutory or jealous content). Third, on the basis of both historical tradition (1) and research findings (e.g., 2, 3), negative or deficit symptoms were given more emphasis by moving the item on affective changes from a subsidiary position in *DSM-III* (A-6-a) (of significance only when formal thought disorder was present) to its position in *DSM-III-R* (A-1-e), where it is coequal with delusions, hallucinations, thought disorder, and catatonic behavior.

Fourth, the definition of bizarre delusion was changed from *DSM-III* ("content which is patently absurd and has no possible basis in fact") to *DSM-III-R* ("involving a phenomenon that the person's culture would regard as totally implausible"). The *DSM-III*

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definition, which focused on the physical impossibility of the delusional belief, was felt to be inadequate because 1) in our high-technology world, the boundaries of the impossible are shrinking (e.g., a person *could* have had a radio receiver implanted in his or her teeth during a dental procedure, people do have machines for hearts), 2) from a historical perspective, the key feature of schizophrenic delusions has been their marked departure from consensual reality (or their lack of understandability [4]) rather than their physical impossibility, and 3) a culture-free definition of bizarreness is difficult to defend, since what would not be bizarre in one culture (e.g., spirit possession) could be bizarre in another. The *DSM-III-R* definition of bizarre delusion was developed in an attempt to address these limitations.

Finally, *DSM-III* contained no duration requirement for criterion A. Although this is rarely a clinical problem, it is theoretically possible that schizophrenia could be diagnosed in an individual who had met criterion A for only several hours. Because the clinical concept of schizophrenia required sustained psychotic symptoms, *DSM-III-R* requires the presence of one or more criterion A items for at least 1 week, except in the rare instance in which the active psychotic symptoms respond to treatment within 1 week of onset.

Other Criteria

In *DSM-III* criterion B reads simply "deterioration from a previous level of functioning in such areas as work, social relations, and self-care." This definition posed problems for early-onset cases of schizophrenia, especially those involving individuals with poor premorbid functioning, since such individuals might never have achieved a substantial level of psychosocial functioning from which to deteriorate. Therefore, in *DSM-III-R*, this criterion was broadened to include "failure to achieve expected level of social development."

In *DSM-III* affective disorders were excluded from the diagnosis of schizophrenia by criterion D: "The full depressive or manic syndrome, if present, developed after any psychotic symptoms, or was brief in duration relative to the duration of the psychotic symptoms in A." This criterion (now C in *DSM-III-R*) was changed in three ways. First, the language was changed to require that mood disorder with psychotic symptoms and schizoaffective disorder be actively ruled out. Second, the *DSM-III* criterion implied that schizophrenia should not be diagnosed if a full affective syndrome preceded the onset of psychotic symptoms. This criterion was eliminated because the descriptive literature back to Kraepelin has stressed that a depressive syndrome is common in the prodromal phases of schizophrenia but usually fades rapidly thereafter (1). If the affective symptoms do not fade, their significance would be recognized because they would not be brief relative to the duration of the psychotic symptoms. Third, by considering only the overlap of mood symptoms with the *active* phase of schizophrenia (e.g., when the illness meets criterion A), *DSM-III* would eliminate from the diagnosis of schizophrenia the following case: An individual had 6 weeks of active A symptoms, during the first two of which he also displayed a prominent depressive syndrome, followed by 2 years of marked residual symptoms and considerable impairment but no mood disturbance. In *DSM-III* the disorder of schizophrenia is considered to consist of *both* active and prodromal/residual phases. Therefore, it seemed illogical to exclude cases in which the affective features were prominent during what may be a very small proportion of the total illness period. In *DSM-III-R* criterion C reads in part "the total duration of all episodes of a mood syndrome has been brief relative to the total duration of the active and residual phases of the disturbance."

In accord with increased interest in negative symptoms in schizophrenia, one prodromal/residual symptom was added in *DSM-III-R* (D-9: "marked lack of initiative, interests, or energy") and reflects the key concept of avolition emphasized by Kraepelin (1). This symptom is common in schizophrenia and can be reliably assessed (2, 3, 5). In addition, to emphasize the severity of the prodromal/residual symptoms required to meet the criteria, the term "marked" was added to symptoms 1–4.

As in the rest of *DSM-III-R*, the old *DSM-III* criterion F for schizophrenia (not due to an organic mental disorder or mental retardation) was changed to (*DSM-III-R* criterion E) "It cannot be established that an organic factor initiated and maintained the disturbance." The *DSM-III-R* criterion is, we think, clearer and easier to use in a clinical setting. This is particularly true for cases in which drug abuse may have played some role in the onset of schizophrenia, but the illness has long persisted in the absence of further abuse. With the *DSM-III-R* criteria, such cases, which appear from a familial perspective to be closely related to typical schizophrenia (6), can be so diagnosed.

In *DSM-III* it was possible for an adolescent or adult who had a childhood diagnosis of infantile autism to meet criteria for schizophrenia on the basis only of typical autistic abnormalities in affect and thought. Because blurring of diagnostic boundaries between these two conditions was felt to be undesirable, criterion F was added to *DSM-III-R* so that an individual with a history of autistic disorder could be diagnosed as schizophrenic only if prominent delusions or hallucinations were present.

Age at Onset

Criterion E for schizophrenia in *DSM-III* ("onset of prodromal or active phase of illness before age 45") was originally proposed as an attempt to increase homogeneity in this diagnostic category. Although continuity with *DSM-III* was maintained by having all cases meeting criteria for schizophrenia with age at onset after age 45 designated as late-onset, criterion E was eliminated from *DSM-III-R* for three reasons.

First, aside from the Washington University criteria for schizophrenia (7) (in which onset before age 40 is an optional criterion), there was no historical precedent for this age restriction. By contrast, an old descriptive literature (e.g., 8, 9) that has been recently added to (e.g., 10, 11) emphasizes the phenomenologic continuity between earlier and late-onset schizophrenia. Second, because of the gender differences in age at onset of schizophrenia (e.g., 12), any such age restriction preferentially eliminates females (13).

Third, the available empirical literature does not support an etiologic discontinuity between early and late-onset schizophrenia. Age-at-onset curves in schizophrenia do not consistently show bimodality with a second peak above age 45 (e.g., 14, 15). Family studies suggest that relatives of individuals with late-onset schizophrenia are at considerably higher risk for schizophrenia than the general population (8, 16). An affected sib-pair study that specifically evaluated *DSM-III* criteria for schizophrenia (17) found no difference in the distribution within sibships of cases of schizophrenia with onset before or after age 45.

Subtypes of Schizophrenia

Of the five subtypes in *DSM-III-R*, three (catatonic, undifferentiated, and residual) are basically unchanged from *DSM-III*. However, the criteria for paranoid schizophrenia underwent major changes from *DSM-III* to *DSM-III-R*. The restriction of delusions to those with persecutory, grandiose, and jealousy themes and of hallucinations to those with persecutory or grandiose content was eliminated. Since Kraepelin, the paranoid subtype has been associated with prominent delusions and hallucinations but without a restriction to any particular theme (1). For example, somatic-hypochondriacal delusions were considered particularly common (1).

While *DSM-III* contained no exclusion criteria for paranoid schizophrenia, *DSM-III-R* requires that, in addition to prominent delusions and/or hallucinations, individuals with paranoid schizophrenia have "*none* of the following: incoherence, marked loosening of association, flat or grossly inappropriate affect, catatonic behavior, grossly disorganized behavior." The impetus for this change was a series of studies comparing *DSM-III* criteria for subtyping schizophrenia with those proposed by Tsuang and Winokur and others (18–21). In the Tsuang-Winokur criteria (18), paranoid schizophrenia is diagnosed only in cases without prominent hebephrenic or catatonic features. Compared to *DSM-III* paranoid schizophrenia, paranoid schizophrenia defined by the Tsuang-Winokur criteria was slightly more reliable (19), was slightly more stable over time (20), and had a much better long-term social outcome (21). Cases diagnosed as paranoid by *DSM-III* but *not* by the Tsuang-Winokur criteria were indistinguishable on long-term outcome from all nonparanoid cases. Therefore, because it was judged better to define a smaller but more homogeneous group, the criteria for paranoid schizophrenia in *DSM-III-R* were modeled after those proposed by Tsuang and Winokur.

One important change was introduced in the disorganized subtype. While *DSM-III* provided no rule for cases meeting criteria for both catatonic and disorganized subtypes, in *DSM-III-R* disorganized subtype can be assigned only to individuals not meeting criteria for the catatonic subtype. With the new criteria for the paranoid subtype, *DSM-III-R* creates a functional hierarchy for the four major subtypes of schizophrenia: catatonic, disorganized, paranoid, and undifferentiated.

DELUSIONAL (PARANOID) DISORDER

Major changes were made in this section from *DSM-III* to *DSM-III-R*. The term "paranoid," which has a long history in psychiatry (22), is used in English-speaking countries in four different ways: to refer to a cognitive style (e.g., suspicious), a type of delusion (e.g., persecutory), a subtype of schizophrenia, and a type of psychotic disorder (e.g., paranoid disorder). However, an individual with an illness that would historically have been called "paranoid disorder" might have a single grandiose delusion, might not be suspicious, nor have persecutory delusion or suffer from a subtype of schizophrenia. After the advantages of conceptual clarity versus historical continuity were weighed, the decision was made to adopt for this category the term "delusional disorder" (23). This name succinctly summarizes the central psychopathologic feature of this diagnostic category: the presence of delusions not due to a schizophrenic, mood, or organic mental disorder.

In *DSM-III* the diagnosis of paranoid disorder could only be applied to people with delusions of persecution or jealousy. However, from the time of Kraepelin (24), a descriptive literature has accumulated on patients presenting with a "paranoid disorder-like" picture but with grandiose, somatic, erotomanic, and referential delusions. No historical precedent was available for the restriction of this diagnostic category to cases with only persecutory and jealousy delusions.

In addition, the small available empirical literature does not support the restrictive *DSM-III* approach to this disorder. Three Scandinavian follow-up studies have examined the relationship between delusional theme and outcome in cohorts of patients with mixed, nonaffective psychoses (25–27). If certain types of delusions were specific for schizophrenia, then the presence of such delusions should predict a schizophrenic outcome, whereas delusions considered specific for paranoid disorder should predict a nonschizophrenic outcome. However, these studies revealed no consistent relationship between delusional theme and the follow-up diagnosis of schizophrenia (28). A recently completed further follow-up in one of these cohorts (29) revealed a similar lack of association between delusional theme at admission and schizophrenic outcome. Finally, a small-sample, family history study of patients who met criteria very similar to those in *DSM-III-R* for delusional disorder found no difference in the pattern of illness in relatives of those who did versus those who did not also meet the more restrictive *DSM-III* criteria for the disorder (30).

Therefore, consistent with historical tradition and the available empirical literature, the major symptomatic inclusion criteria for delusional disorder in *DSM-III-R* require only the presence of one or more nonbizarre delusions, without further specification. In accord with the definition of bizarre delusions, the term "nonbizarre delusions" was defined as involving phenomena that would not be considered totally implausible in the individual's culture. That is, although it may be clear clinically that the beliefs are delusional, the delusions in this disorder involve situations that *can* occur in real life. *DSM-III-R* provides a list of such situations in a Western culture: "being followed, poisoned, infected, loved at a distance, having a disease, [or] being deceived by one's spouse or lover."

Two other significant changes were made in the criteria for delusional (paranoid) disorder in *DSM-III-R*. First, the minimum duration of illness was increased from 1 week to 1 month. Since many cases of brief reactive psychosis involve nonbizarre delusions, it was judged important to clarify, from a temporal perspective, the boundary between this syndrome and delusional (paranoid) disorder. Second, criterion E in *DSM-III* ("no prominent hallucinations") was changed (criterion B in *DSM-III-R*) to "auditory or visual hallucinations, if present, are not prominent." This was done because tactile and somatic hallucinations (usually of infestation) are common in somatic delusional disorder syndromes (31), while olfactory hallucinations (usually of alimentary or vaginal stench) are often present in the olfactory reference syndrome (32, 33).

DSM-III provided a subdivision of paranoid disorder by duration of illness: greater than 6 months—paranoia, less than 6 months—acute paranoid disorder. In *DSM-III-R* this temporal subdivision was replaced by one based on prominent delusional theme: erotomanic, grandiose, jealous, persecutory, somatic, and unspecified. Little research literature was available to support this temporal division of delusional (paranoid) disorder. Furthermore, with the increase in the minimum duration of the disorder to 1 month, the category of acute paranoid disorder became less viable as a diagnostic entity.

PSYCHOTIC DISORDERS NOT ELSEWHERE CLASSIFIED

DSM-III-R lists four major disorders in this category: brief reactive psychosis, schizophreniform disorder, schizoaffective disorder, and induced psychotic disorder. The residual category (psychotic disorder not otherwise specified [atypical psychosis] in *DSM-III-R*) will not be discussed here, since it is without criteria and underwent no significant change from *DSM-III* to *DSM-III-R*.

Brief Reactive Psychosis

Three important changes in the criteria for this diagnosis were introduced in *DSM-III-R*. First, in order to approximate more closely the Scandinavian concept of reactive psychosis, the maximum duration was increased from 2 to 4 weeks. Second, unlike *DSM-III*, *DSM-III-R* requires that the psychotic symptoms occur "apparently in response to" stressful events. That is, in addition to the chronologic relationship between the stressful event and the psychosis, as required in *DSM-III*, *DSM-III-R* requires the clinical judgment that there is a causal relationship between the stressful events and the psychosis. Third, *DSM-III* requires a single psychosocial stressor. However, *DSM-III-R* also permits a pattern that is apparently common in non-Western societies: The precipitant is a series of events, no one of which is highly stressful, but all of which, in juxtaposition to one another, become overwhelming.

The final new criterion in *DSM-III-R* brief reactive psychosis (criterion D) eliminates from the diagnostic category individuals manifesting either prodromal symptoms of schizophrenia or schizotypal personality disorder. This criterion was added because the essence of brief reactive psychosis was considered to be a short psychotic episode in an individual who does not have the vulnerability to schizophrenia or schizophrenia-like conditions.

Schizophreniform Disorder

In *DSM-III*, the core feature of schizophreniform disorder was that of a schizophrenia-like illness of less than 6 months' duration. While this essential criterion was not altered in *DSM-III-R*, four other significant changes were made in this diagnostic category. First, *DSM-III* requires that cases of schizophreniform disorder must meet "all criteria for schizophrenia except for duration." In *DSM-III-R* this has been changed to "meets criteria A and C for schizophrenia." The significance of the change is that cases of schizophreniform disorder no longer need to meet the "deterioration" criterion for schizophrenia (criterion B). Given the brief nature and good outcome of many cases of schizophreniform disorder, it was felt to be conceptually inconsistent and clinically unreasonable to require deterioration in functioning for the diagnosis.

The second major change was to introduce a hierarchical relationship between schizophreniform disorder and brief reactive psychosis. In *DSM-III-R* schizophreniform disorder cannot be diagnosed in cases that meet the criteria for brief reactive psychosis. This change was made to clarify the clinical boundaries between these two conditions and provide a rule for diagnosing the better prognosis disorder when criteria for both might be met.

Third, *DSM-III-R* introduces a subdivision of schizophreniform disorder into cases with and without good prognostic features. The term "schizophreniform disorder" was first applied by Langfeldt to a group of schizophrenia-like conditions with a tendency toward good outcome (34). It continues to retain this meaning in most of Europe. As conceptualized in *DSM-III*, however, this diagnosis was defined *only* by duration. Four good prognostic features were added in *DSM-III-R* to permit the identification of a subgroup of cases with schizophreniform disorder that would more closely approximate Langfeldt's original concept. The four criteria were chosen from a large descriptive literature as those that most consistently predicted good outcome in individuals presenting with broadly defined schizophrenia (e.g., 34–43). Three of the four proposed criteria (acute onset, "cloudiness" of consciousness, and good premorbid functioning) were emphasized by Langfeldt in his original monograph (34).

The final change in schizophreniform disorder in *DSM-III-R* is the requirement that the diagnosis be considered provisional in individuals who have not yet recovered. This requirement stems from the observation that a substantial proportion of individuals who meet the criteria for schizophreniform disorder, but have not yet recovered, will eventually go on to meet the criteria for schizophrenia (44). Therefore, from both a clinical and research perspective, it is important to know whether individuals with schizophreniform disorder have recovered within 6 months or are still ill and may yet progress to schizophrenia.

Schizoaffective Disorder

Schizoaffective disorder, which has been among the most controversial categories in psychiatry, was unique among major psychiatric syndromes in having no specific criteria in *DSM-III*. Because this was uniformly considered undesirable, and because considerable information had accumulated on this condition since the development of *DSM-III*, criteria for schizoaffective disorder were proposed for *DSM-III-R*. There have been several different conceptual approaches to schizoaffective disorder since the entity was first described by Kasanin (45); most of these approaches can be classified as either cross-sectional or longitudinal. In *DSM-III*, largely as a result of the influential article of Pope and Lipinski (46), cross-sectional schizoaffective disorder (i.e., in which prominent schizophrenia-like symptoms occur only *at the same time* as a full affective syndrome) is classified as a mood-incongruent psychotic form of affective disorder.

Although the subject of some debate, *DSM-III-R* maintained the classification of cross-sectional schizoaffective disorder as a subtype of affective illness. Therefore, a viable definition of schizoaffective disorder as an independent category would have to take a longitudinal approach to the disorder. The specific approach taken, which derives from the "mainly schizophrenic" schizoaffective disorder of the Research Diagnostic Criteria (RDC) (47), gives the diagnosis of schizoaffective disorder to individuals who have had episodes with both schizophrenic symptoms and a full affective syndrome but who, at other times in their illness, have had clear psychotic symptoms for 2 weeks or more *in the absence* of prominent affective features.

A substantial body of research has accumulated which suggests that, when defined in this way, schizoaffective disorder is not likely to be a subtype of affective illness and *may* have a close relationship with typical schizophrenia. This research can be divided into three kinds: follow-up, treatment, and family/genetic. Himmelhoch et al. (48) studied a large population of patients with affective disorders who also displayed psychotic symptoms. The subgroup who had psychotic symptoms between episodes of affective illness differed from all other groups in having poor interpersonal relationships, poor response to treatment, a higher relapse rate, and a tendency toward deterioration over time. Brockington et al. (49) studied a broad group of "schizodepressive" patients and found that one of the most powerful predictors of a poor, schizophrenia-like outcome was "the presence of schizophrenic symptoms at some time without depression."

Mattes and Nayak (50) compared lithium and fluphenazine in a double-blind trial in mainly schizophrenic schizoaffective patients, defined by the RDC. Lithium was significantly worse than fluphenazine in preventing relapse. These results are broadly consistent with those of Maj (51), who found lithium to be relatively ineffective in schizoaffective patients with prominent schizophrenic symptoms.

Family/genetic studies have probably provided the most convincing evidence that schizoaffective disorder, as defined in *DSM-III-R*, is more closely related to schizophrenia than to affective illness. In one study of affected pairs of siblings (17), the distribution of cases of schizoaffective disorder resembled that found for schizophrenia but not for affective illness. In the large Iowa 500/non-500 cohort, the risk for schizoaffective disorder was significantly greater in relatives of schizophrenic subjects than in control probands (52). Two family studies and one adoption study have examined the risk for schizophrenia and affective illness in biological relatives of probands with *DSM-III-R*-like schizoaffective disorder (44, 53, 54). All three studies found significantly high risks for schizophrenia and/or schizotypal personality disorder in relatives of probands with schizoaffective disorder. Neither of the two studies with normal control probands (44, 54) found a higher risk for affective illness in relatives of probands with *DSM-III-R*-like schizoaffective disorder than in relatives of control subjects. In both studies that contained a group of probands with affective disorder (44, 53), the risk for affective illness was significantly less in relatives of probands with schizoaffective disorder than in relatives of probands with affective disorder. Of particular interest, two of these studies (44, 53) applied the RDC to subdivide subjects with broadly defined schizoaffective disorder into those who met criteria for the mainly schizophrenic subtype (on which *DSM-III-R* criteria for schizoaffective disorder were based) and those who did not. In both studies, this division appeared to make sense from a familial perspective. For example, a substantially high risk for affective illness in both samples was seen only in relatives of the schizoaffective probands who *did not* meet the criteria for the mainly schizophrenic subtype.

The *DSM-III-R* criteria for schizoaffective disorder are unlikely to be the final word on this controversial category. Space prohibits a full review of all the literature in this area, and while most studies are consistent with the results reviewed above, this is not universally true. One sib-pair study (55) and one family study (56) available after the completion of *DSM-III-R* are not fully in accord with the results reviewed above; both suggest differences in familial loading between patients with schizophrenia and *DSM-III-R*-like schizoaffective disorder. Interestingly, two studies have recently challenged the inclusion of all cases of cross-sectional schizoaffective disorder in the major affective disorders. If such cases are defined as meeting, concurrently, the full RDC or *DSM-III* criteria for *both* schizophrenia and affective illness (rather than just having some schizophrenic features with a full affective syndrome), both studies have found that from the perspective either of outcome (57) or familial psychopathology (58), such cases resemble typical schizophrenia and not typical affective illness.

DSM-III-R specifies that cases of schizoaffective disorder should be subdivided into bipolar or depressive types. Considerable evidence suggests that when schizoaffective disorder is broadly defined (i.e., to include many cross-sectional cases), the bipolar type is more closely related to affective illness than is the depressive type (e.g., 49, 59, 60). However, to our knowledge, only one published study has examined this subdivision when applied to the more narrowly defined schizoaffective disorder proposed in *DSM-III-R*. Kendler et al. (44) found that from a familial perspective, patients who met the *DSM-III-R*-like criteria for schizoaffective disorder, bipolar type, resembled cases of schizophrenia and not cases of affective illness. These results, which are congruent with the conclusions of a recent thorough review article (61), suggest that mainly schizophrenic bipolar schizoaffective disorder is not a subtype of affective illness.

Induced Psychotic Disorder

This diagnosis (the modern equivalent of the folie imposée subtype of folie à deux) was classified in *DSM-III* as a subtype of paranoid disorder termed shared paranoid disorder. Therefore, it could only be applied to cases in which the delusion was nonbizarre and had a theme of either persecution or jealousy.

Since its inception, the essence of this syndrome has been the "transmission" of delusional beliefs from one individual (the primary case) to another (the secondary case), usually as a result of sustained and intimate contact (62–64). The nature and theme of the transmitted delusion have been variable and have depended largely on the diagnosis of the primary case. Although no detailed data are available, the most common diagnosis in primary cases is probably paranoid schizophrenia, followed by delusional (paranoid) disorder and delusional affective illness (63, 64). Although persecutory delusions appear to be particularly common, grandiose, religious, and somatic delusions have also been transmitted (63). From the historical perspective, the *DSM-III* definition of shared paranoid disorder was overly restrictive.

Therefore, in *DSM-III-R* any delusion that has been transmitted will meet the criteria for what is now termed "induced psychotic disorder." Since neither the etiology nor the clinical presentation of this syndrome is necessarily closely related to delusional (paranoid) disorder, in *DSM-III-R* the category of induced psychotic disorder is now in the category of psychotic disorders not elsewhere classified.

PROPOSED CHANGES NOT INCORPORATED INTO *DSM-III-R*

While most of the changes in the psychotic disorders section in *DSM-III-R* were made with a consensus of those involved, this was not always the case. Two controversies were notable and worthy of review to provide a sense of the issues on which consensus was lacking and to provide examples of the approach taken to controversial nosologic issues.

A Category of Schizophrenia and Related Disorders

This proposal suggested a reorganization of the psychotic disorders section to create a category of schizophrenia and related disorders, which would include schizophrenia, schizoaffective disorder, and schizophreniform disorder. The unifying phenomenologic basis of this category would be criteria A for schizophrenia, met by all cases in these three diagnostic categories. This proposal would create a family of psychotic disorders with a common phenomenologic core that *might* indicate an etiologic interrelationship and would be broadly analogous to the family of mood or anxiety disorders. As noted above, much current evidence suggests that schizoaffective disorder, as defined in *DSM-III-R*, has a close relationship with schizophrenia. Less evidence, however, is available regarding schizophreniform disorder. Cases meeting the criteria for this category tend to have a better outcome than typical cases of schizophrenia (65–68). Of the three fairly recent family studies of schizophreniform disorder, two (44, 66) support and one (69) does not support a close familial relationship between schizophrenia and schizophreniform disorder. Patients with schizophreniform disorder may be more likely to respond to lithium than those with schizophrenia (70).

There was disagreement as to whether this proposal constituted a major or minor nosologic change. Proponents of the proposal emphasized the practical utility for both the clinician and researcher of grouping these disorders together. Opponents felt that such a grouping should only be made if compelling evidence were available for the etiologic interrelationship of the three disorders. Resolution was not reached about either the conceptual and practical advantages of the proposal or the magnitude of its empirical support. The final decision was to leave schizoaffective and schizophreniform disorders in the category of psychotic disorders not elsewhere classified and to recommend that the issue be reconsidered during the development of *DSM-IV*.

Proposed Reduction in the Required Duration of Schizophrenia

This proposal, which sought to eliminate the prodromal symptoms from the criteria for schizophrenia and to reduce the required duration from 6 to 2 months, was supported by several arguments. First, in clinical and epidemiologic settings, the retrospective assessment of prodromal symptoms, particularly in new-onset cases, was considered to be difficult and of questionable reliability. Second, this approach more closely approximated that taken in the draft criteria for *ICD-10* (71). Third, it was argued that defining a wider category of illness, rather than a priori restricting the disorder to more chronic cases, would aid clinicians and researchers in identifying heterogeneity in schizophrenia-like disorders.

Because discussion of the broad issues raised by the second and third arguments is beyond the scope of this article, we will focus on the key empirical issue raised by this proposal: the reliability and validity of the 6-month duration criterion for schizophrenia, including prodromal symptoms. The proponents of this proposal were particularly concerned with how *DSM-III* criteria would work in new-onset cases. Because very little information is available in such populations, we review these issues more generally.

We are aware of one report that evaluated the cross-sectional reliability of the specific *DSM-III* prodromal/residual symptoms in a series of consecutively admitted schizophrenic patients (72). This sample almost certainly contained only a small proportion of new-onset cases and therefore does not fully address a central issue in the proposal. The mean±SD kappa value (i.e., chance-corrected agreement) for these eight symptoms was 0.49±0.29, indicating only moderate reliability. The low mean kappa was largely the result of three items (items 5—flat affect, 6—vague speech, and 8—unusual perceptions) that had very poor reliability (kappa<0.15). We are unaware of any study that has assessed the reliability of the retrospective assessment of duration of prodromal symptoms.

We found two reports on the reliability of the 6-month criterion for schizophrenia, both from cross-sectional samples of patients, which indicate high reliability with kappa values of 0.69 (72) and 1.00 (73). We are aware of seven reports on the reliability of the *DSM-III* diagnosis of schizophrenia in clinical populations in which both diagnoses were made with the same assessment method (table 1). Although none of these studies is devoid of limitations, and none specifically examines new-onset cases, they suggest that in diverse settings with typical patient samples, the interrater reliability of *DSM-III* schizophrenia is good to excellent.

TABLE 1. Studies Reporting Interrater Reliability for the *DSM-III* Diagnosis of Schizophrenia

Study	Total Cohort	Schizophrenic Patients	Kappa	Comments
Spitzer et al. (74): *DSM-III* field trials				
Phase 1	339	60	0.81	Patient interview
Phase 2	331	71	0.81	Patient interview
Endicott et al. (72)	65	12	0.80	Patient interview
McGlashan (75)	75	—	0.66	Review of chart abstracts; number of cases of schizophrenia not stated
Kendler and Gruenberg (54)	20	6	1.00	Review of interview protocols
Folstein et al. (73)	70	14	1.00	Videotapes
Fuhrer et al. (76)	—	—	0.79	136 French psychiatrists reviewed 11 videotapes
Kulhara et al. (77)	112	56	0.61	Interview of patients with an *ICD-9* diagnosis of schizophrenia

Since the validity of the *DSM-III* criteria for schizophrenia has been reviewed by one of us in detail elsewhere (78), we will be brief here. We are aware of six studies that examined the outcome of schizophrenia as defined by *DSM-III* versus that defined by other criteria sets. Five of these studies (42, 65, 79–81) found and one (82) did not find that the *DSM-III* criteria were able to select patients with a relatively poor prognosis. Two studies compared the diagnostic stability of schizophrenia as defined by *DSM-III*, compared with other systems. Both (65, 80) found schizophrenia as diagnosed by *DSM-III* to be at least as stable as, if not more stable than, schizophrenia diagnosed by other systems. Two reports based on short- and long-term follow-up of the same patient cohort (66, 67) evaluated a critical question raised by this proposal: the relationship between duration of illness and outcome. The short-term follow-up suggested a large difference in outcome between those ill less than versus more than 1 month (66). In the long-term follow-up, however, there was only a graded positive relationship between longer duration of illness and poorer outcome (67).

Does the 6-month criterion for schizophrenia work only because prior chronicity predicts future chronicity? Two studies have addressed this important question. Helzer et al. (83) found that the outcome of patients meeting *DSM-III* criteria for schizophrenia was consistently and significantly worse than that of patients who, although ill at index admission for more than 6 months, failed to meet *DSM-III* criteria for schizophrenia. Loyd and Tsuang (84) found that the 6-month criterion predicted poor outcome when applied to patients with schizophrenia, but *not* when applied to patients with affective illness. The joint occurrence of *both* schizophrenic symptoms and chronicity of illness appears to be important in defining poor outcome in *DSM-III* schizophrenia.

Finally, the validity of *DSM-III* schizophrenia can be evaluated from a familial/genetic perspective. In a recent large family study, the degree of familial aggregation of schizophrenia, as defined by *DSM-III*, was no greater than that found for a much broader definition of schizophrenia (all nonaffective psychotic disorders in *DSM-III*) (52). As reviewed above, *DSM-III* schizophrenia may have a close familial relationship with *DSM-III-R*-like schizoaffective disorder and possibly with schizophreniform disorder (17, 44, 52–54, 58, 66).

To summarize, the *DSM-III* criteria for schizophrenia appear to succeed reasonably well at identifying a diagnostically stable, poor outcome group, and both the specific symptoms and the duration criteria are required for this. Three of eight prodromal-residual symptoms, when assessed cross-sectionally, appear to have low reliability, although the 6-month criterion and the diagnosis as a whole appear relatively reliable in typical patient cohorts. From a familial perspective, *DSM-III* schizophrenia may be defined too narrowly. While the 6-month criterion appears to function reasonably well in terms of reliability and validity in general patient populations, we know very little of how it performs in first-onset cases or how an alternative criterion of 2, 4, or 12 months would compare. Work is clearly needed to develop more reliable residual/prodromal symptoms, to test them in new onset cases, and to examine the reliability and validity of alternative duration requirements for schizophrenia.

This proposal suggests an important change in a major diagnostic category. A review suggests that there is little empirical information available to specifically evaluate the proposal. In general, from the perspective of both reliability and validity, the current *DSM-III* criteria are functioning relatively well. Therefore, the final decision was made to retain both the prodromal symptoms and the 6-month duration criterion for schizophrenia in *DSM-III-R*.

COMMENT

Changes made in the *DSM-III-R* psychotic disorders ranged from relatively minor (e.g., schizophrenia) to major (e.g., delusional disorder). The rationale for these changes can be usefully divided into three groups. The first is changes made, without empirical support, either as conceptual clarifications (e.g., the reorganization of criterion A for schizophrenia) or in response to deficiencies in *DSM-III* perceived from a clinical and/or historical perspective (e.g., the extension of brief reactive psychoses from 2 weeks to 1 month and the changes in induced psychotic disorder). The second category is similar to the first except that some empirical evidence was available to guide and evaluate the proposed changes (e.g., changing the kind of delusion required for paranoid disorder, eliminating the age 45 cutoff for schizophrenia, and adding the good prognostic features to schizophreniform disorder). The third kind of change was motivated mainly by advances made in empirical data (although the interpretation thereof was not always free of controversy). The best examples of this kind of change were the proposed criteria for schizoaffective disorder and the change in the criteria for paranoid schizophrenia.

It is our hope that in the preparation of the psychotic disorders section of *DSM-IV*, most changes will be of the second and third variety. We see as a central goal for future *DSM* revisions that they become increasingly empirically based. Revisions of the first type, although needed during a "shakedown" process in the nosology, are inevitably sensitive to changes in committee membership and idiosyncratic interpretations of clinical and historical trends. Both to provide the necessary stability *and* to gradually increase the scientific basis for our nosologic system, an increasingly rigorous and data-based revision process is needed.

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Neurochemical Abnormalities of Anorexia Nervosa and Bulimia Nervosa

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The authors review the research on anorexia nervosa and bulimia nervosa, emphasizing the neurotransmitters and neuromodulators that regulate eating behavior. Anorexia nervosa is associated with changes in the noradrenergic, serotonergic, and opioid systems; bulimia nervosa is accompanied by marked alterations in serotonin and norepinephrine activity. These neurochemical changes may perpetuate pathological eating behavior and may be responsible for several associated psychiatric symptoms, including anxiety and depression. The authors also summarize studies of several drugs that are used in the treatment of eating disorders and are known to modify neurotransmitter activity. Understanding the neurochemistry of eating disorders seems crucial for the rational development of both psychopharmacological and behavioral treatments.

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Anorexia nervosa and bulimia nervosa are syndromes characterized by gross disturbances in eating behavior that share underlying concerns for dieting and weight regulation.

According to *DSM-III-R,* anorexia nervosa is characterized by refusal to maintain body weight over minimal norms, weight more than 15% below expected body weight, intense fear of gaining weight or becoming fat, disturbance of body image, and, in females, absence of at least three consecutive expected menstrual cycles.

Bulimia nervosa, according to *DSM-III-R,* involves recurrent episodes of binge eating occurring at least twice a week for 3 months, a feeling of lack of control over eating behavior during the binges, persistent overconcern with body shape and weight, and the use of self-induced vomiting, laxatives, diuretics, dieting, or vigorous exercise to prevent weight gain.

Although these two disorders are considered to be two distinct entities, stringent attempts by patients with anorexia nervosa to limit food intake may be interrupted at times by episodes of bulimia; it also appears that the proposed distinction between bulimic patients with and without anorexia nervosa is not supported by a rigorous analysis of their demographic, clinical, and psychometric features (1). Therefore, it is quite possible that psychoneuroendocrinological correlates of these two disorders may overlap.

Neurochemical alterations may have a pathophysiological role in these disorders. Several CNS neurotransmitters and neuromodulators are known to be involved in the regulation of eating behavior in animals and have been implicated in symptoms such as depression and anxiety often observed in patients with eating disorders. Since neurochemical changes in patients with anorexia nervosa or bulimia nervosa may precede, accompany, or follow behavioral changes, it is difficult to assess what role these changes play in the etiology and maintenance of these disorders. The effects of weight loss on the CNS are quite marked and may confound the interpretation of the data. The study of neurochemical alterations in eating disorders can delineate secondary endocrine and metabolic changes that represent some of the biochemical substrates for the physical complications in anorexia nervosa and bulimia nervosa and may, in turn, facilitate and reinforce abnormal patterns of eating behavior. Neurochemical research may also contribute to understanding the pathophysiology of eating disorders, and this knowledge could potentially benefit various nonsomatic (e.g., behavioral and psychotherapeutic) treatment modalities in addition to leading to the development of more successful psychopharmacological treatment for these disorders.

In this paper, we will review studies on noradrenergic, serotonergic, dopaminergic, and opioid systems; on the neuromodulators corticotropin-releasing hormone (CRH), vasopressin (antidiuretic hormone) (ADH), and cholecystokinin; and on some brain metabolic and morphologic measures in patients with eating disorders. Furthermore, we will highlight some of the studies on drug therapy of eating disorders with

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reference to the effects of these agents on neurotransmitters and neuromodulators.

NEUROTRANSMITTER SYSTEMS

Noradrenergic

The noradrenergic system has been implicated in the pathogenesis of anorexia nervosa (2) and is likely to be involved in the physiological regulation of feeding behavior at the CNS level (3). For example, application of α_2-adrenergic agonists to the paraventricular nucleus of the rat hypothalamus produces pronounced hyperphagia (4), and application of β-adrenergic agonists to the perifornical region of the hypothalamus inhibits feeding (5). Several studies suggest that the noradrenergic system provides important neural substrates for anxiety (6) and depression (7). These affective states are observed frequently in patients with anorexia nervosa and bulimia nervosa (8). Activation of the locus ceruleus, the major norepinephrine cell group in the mammalian brain, may be associated with anxiety (9); starvation may decrease central and, in particular, locus ceruleus norepinephrine activity with subsequent reduced anxiety (10). Decreased sympathetic activity may also decrease metabolic rate (11) and protect the anorexia nervosa patient by decreasing nutrient requirements.

Central norepinephrine metabolism has been extensively studied in anorexia nervosa either directly by looking at CSF concentrations of norepinephrine and/or its major metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), or indirectly by measuring peripheral (plasma or urinary) MHPG concentrations, which partly reflect central norepinephrine metabolism. Studies of patients with anorexia nervosa (2, 12–19) have consistently found lower than normal concentrations of urinary and plasma MHPG and of CSF norepinephrine and MHPG, suggesting that norepinephrine turnover is reduced in anorexia nervosa. This finding may be secondary to the starvation state, since plasma norepinephrine and urine MHPG levels increase to near-normal levels after weight gain (12). In addition, urinary MHPG excretion is best predicted by percentage of body fat in both normal and anorectic women (19). When patients with anorexia nervosa are studied after mild nutritional rehabilitation (20) or in the early stages of weight gain, norepinephrine and MHPG values tend to be in the normal range (21). However, anorectic patients who have recovered their normal weight for a mean±SD of 20±7 months had a 50% lower CSF norepinephrine level than normal control subjects (20); therefore, a pervasive defect in norepinephrine metabolism may be a "trait" marker of anorexia nervosa.

Indirect evidence of lower levels of peripheral norepinephrine concentration comes from a greater number of platelet α_2-adrenergic receptor binding sites in patients with anorexia nervosa (17, 22, 23). When these patients regained 10% of their weight, the platelet α_2-adrenergic receptor binding sites stabilized at normal levels (22). Mikhailidis et al. (23) also found greater platelet aggregation and thromboxane A_2 release in response to epinephrine in patients with anorexia nervosa compared with normal control subjects. Following weight gain these responses normalized.

Postsynaptic α_2-receptor activity has been evaluated in patients with anorexia nervosa by examining the growth hormone (GH) response to stimulation with the α_2-adrenergic receptor agonist clonidine. However, the interpretation of this test in patients with anorexia nervosa is complicated by the finding that these patients have an abnormal GH secretion secondary to reduced levels of somatomedin C. The GH response to clonidine challenge was found to be normal in low-weight patients with anorexia nervosa but was diminished during nutritional rehabilitation and weight gain (10). Presynaptic α_2-receptor sensitivity (as assessed by clonidine-induced decreases in plasma MHPG) was found to be higher than normal in low-weight patients with anorexia nervosa but decreased to the normal range during refeeding (10). A higher level of presynaptic inhibitory α_2-adrenergic receptor sensitivity would possibly potentiate a decrease in central norepinephrine release.

Several studies found altered noradrenergic function in bulimia nervosa as well. During the first week after hospital admission patients with bulimia nervosa had a blunted rise in plasma norepinephrine concentration on standing (24). Even after 3 weeks of treatment in a clinical research inpatient unit, without binge eating and purging, these patients had significantly lower resting plasma levels of norepinephrine (25). In addition, bulimic patients had a higher number of platelet α_2-adrenergic receptors (22).

Bulimic patients have a significantly lower resting pulse, systolic blood pressure, and plasma norepinephrine than control subjects. In response to increasing doses of intravenous infusion of the β-adrenergic agonist isoproterenol, patients with bulimia nervosa show greater sensitivity to the chronotropic effects of isoproterenol, reaching a pulse increase of 25 beats per minute at a significantly lower drug dose than control subjects (26). This last finding probably reflects greater sensitivity of cardiovascular β-adrenergic receptors, which may be induced by decreased release of catecholamines.

Serotonergic

Animal studies have shown that serotonin plays an inhibiting role in feeding behavior (27). This neurotransmitter acts on the ventromedial hypothalamus, which is considered a satiety system (27). The relevance of the serotonergic system in eating disorders may be linked to the observation that patients with eating disorders often present with depression, anxiety (8), and obsessive-compulsive features and that this system seems to play an important role in other psychiatric disorders, including depression (28), obsessive-compulsive disorder (29), and anxiety (30).

The results of the studies on serotonergic activity in patients with anorexia nervosa are somewhat conflicting. In fact, although Gerner et al. (21) reported that CSF levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) and of tryptophan, a precursor of serotonin, were no different in patients with anorexia nervosa than in normal control subjects, Kaye et al. (20) found that underweight anorectic patients had CSF 5-HIAA levels that were 20% lower than normal and that these levels normalized after weight recovery. In addition, platelet serotonin uptake did not differ between anorectic patients and normal control subjects (31, 32).

Serotonin metabolism has been extensively studied in patients with bulimia nervosa. Normal-weight bulimic subjects have a blunted L-tryptophan-induced rise of plasma prolactin levels compared with control subjects (33). Bulimic patients who became satiated and stopped binge eating and vomiting had an increase in their plasma L-tryptophan-large neutral amino acids ratio, but the plasma L-tryptophan-large neutral amino acids ratio did not increase in bulimic patients who did not feel satiated by binge eating and vomiting (34). Since large neutral amino acids compete with L-tryptophan for the same carrier system to cross the blood-brain barrier, the plasma L-tryptophan-large neutral amino acids ratio is considered the most important factor determining transport of tryptophan from plasma into the CNS (35). Greater CNS concentrations of L-tryptophan lead to an increase in serotonin synthesis. These observations are consistent with the hypothesis that increased brain serotonin turnover contributes to satiety. Weight-restored anorectic patients with bulimia have been found to have smaller probenecid-induced increases of CSF levels of 5-HIAA than weight-restored nonbulimic anorectic patients, suggesting decreased serotonergic release in bulimia (36).

Dopaminergic

In animal studies, the central administration of low doses of dopamine and dopamine agonists stimulates feeding and administration of higher doses inhibits feeding, probably through the perifornical lateral hypothalamus (3, 37). The dopaminergic system appears to be closely linked to the opioid system in the neuroregulation of eating, since naloxone, an opioid antagonist, inhibits dopamine stimulation of feeding (37) and dopamine antagonists inhibit opioid-stimulated feeding (38).

The results of the studies on dopamine metabolism in anorexia nervosa are inconsistent. In one study (20), underweight anorectic patients had CSF levels of the dopamine metabolite homovanillic acid (HVA) that were 30% lower than normal, but their HVA levels returned to normal shortly after weight recovery. In two other studies (19, 21), however, the CSF level of HVA in underweight anorectic women and normal control subjects did not differ.

Opioid

In animal experiments, naloxone administration decreased feeding in rats following food deprivation (39) and central administration of the endogenous κ-opioid agonists dynorphin and α-neo-endorphin enhanced feeding (37). Moreover, in normal humans, the administration of the κ-opiate agonist butorphanol tartrate can increase food intake (40) and naloxone seems to reduce food intake (41).

Gerner and Sharp (42) found that CSF β-endorphin immunoreactivity among moderately underweight anorectic patients was not different from that of normal subjects. Other researchers found that CSF opioid activity, measured by a radioreceptor assay, was higher in patients with anorexia nervosa than in normal control subjects or in the same patients after weight restoration (43).

Kaye et al. (44) found by radioimmunoassay that levels of β-lipotropin, ACTH, β-endorphin, and the N-terminal fragment of pro-opiomelanocortin in the CSF were significantly lower in extremely underweight anorectic patients but normalized after weight restoration. These authors concluded that a reduction in concentration of these pro-opiomelanocortin peptides occurs as a consequence of weight loss and malnutrition in patients with anorexia nervosa. Furthermore, values of β-endorphin in CSF were found to be less than 1% of the values for total opioid activity measured by the radioreceptor assay; therefore, these pro-opiomelanocortin peptides could not account for the higher levels of CSF opioid activity in anorectic patients (44).

Unfortunately, most of the research studies on bulimia nervosa have examined only peripheral levels of opioids that do not predict central opioid activity. Waller et al. (45) noted that baseline plasma β-endorphin immunoreactivity in bulimic patients was significantly lower than in control subjects. Immunoreactivity also correlated inversely with the severity of bulimic symptoms (45). In contrast, the plasma β-endorphin levels of a smaller group of bulimic subjects were higher than those of control subjects throughout a 5-hour study period and did not respond to glucose ingestion; analysis of variance of repeated measures revealed a significant overall difference between the bulimic subjects and the control subjects (46).

NEUROMODULATORS

CRH

Believed to be the principal substance regulating pituitary corticotropin (ACTH) release, CRH can reduce starvation-induced feeding after central administration in the rat (47). Adrenal demedullation partially diminishes this effect, indicating that the peripheral release of epinephrine may play a role in CRH-induced feeding inhibition (48).

The mean concentration of immunoreactive CRH in the CSF of seven patients with anorexia nervosa was significantly higher than that of 11 subjects with cervical spondylosis (49). CSF levels of CRH in patients with anorexia nervosa were significantly higher than those of normal control subjects but subsequently fell to normal when the patients were fed again. This fall paralleled the normalization of their plasma cortisol levels (50). This is an interesting finding, since higher levels of CSF CRH have also been found in depressed patients in two studies (51, 52) but not in another one (53).

Vasopressin

Since patients with anorexia nervosa often have polyuria, the role of vasopressin in this disorder has been investigated. In four subjects with anorexia nervosa studied before correction of weight loss, the response of plasma arginine vasopressin to hypertonic saline was abnormal (54). In one of these subjects, the plasma concentration of arginine vasopressin increased subnormally relative to the plasma sodium concentration, whereas in the other three it fluctuated erratically with no relation to plasma sodium concentrations. These defects persisted 3 to 4 weeks after recovery of body weight in the three patients studied (54).

Cholecystokinin

Cholecystokinin is a 33-amino-acid polypeptide released from the intestine after eating. Its exogenous administration reduces food intake in rats, sheep, and monkeys, and its slow intravenous infusion reduces food intake in humans (55–57). It appears that both the nucleus tractus solitarius and the paraventricular nucleus of the hypothalamus play important roles in the inhibitory action of systemic cholecystokinin on eating (58, 59).

A recent study (60) showed that both the total integrated plasma cholecystokinin response to a mixed-liquid meal and the postprandial peak plasma cholecystokinin levels were significantly lower in a group of bulimic women than in normal control subjects. Postprandial satiety was also significantly reduced in the bulimic women. In five bulimic patients the satiety response and the postprandial cholecystokinin response to eating increased significantly after an open trial of tricyclic antidepressants (60).

METABOLIC AND MORPHOLOGIC BRAIN CHANGES

Investigators have also considered the role of altered energy metabolism and morphologic changes in the brains of anorectic patients. Positron emission tomography (PET) both during the anorectic state and after weight gain has been used to study regional cerebral glucose metabolism. Caudate metabolism was found to be significantly greater bilaterally during the anorectic state than after weight gain (61). Since a greater percentage of neurons in the caudate nucleus of monkeys responds to the appearance of food in conditioned tasks than after unconditioned stimuli (62), it has been hypothesized that caudate nuclei may play an important role in integrating environmental influences with cognitive processing to form the subject's individual motor response (61). It has also been suggested that global brain hypermetabolism with accentuation in the caudate nuclei may correlate with the clinical observation of greater vigilance and performance in anorectic patients (61).

Morphologic changes in the brain have been documented in patients with anorexia nervosa by transmission computerized tomography (CT) (63, 64). More recently, Krieg et al. (65) showed that 82% of 50 patients with anorexia nervosa had enlarged outer CSF spaces that normalized after weight gain.

DRUG THERAPY OF EATING DISORDERS

Some of the neurochemical abnormalities observed in eating disorders may be particularly relevant to the mechanism of action of those psychotropic drugs which have been used successfully in the treatment of these disorders. In fact, although the mechanism of action of most psychotropic drugs is still unknown, in vitro and in vivo studies have shown that these drugs can affect many neurotransmitter and neuromodulator systems. To date, no drug has been consistently effective in the treatment of anorexia nervosa, including antipsychotic and anticonvulsant drugs (66–68). The best studied and most promising psychotropic agents in bulimia nervosa are the tricyclic antidepressants (desipramine and imipramine) and the monoamine oxidase inhibitors (MAOIs) (phenelzine).

Antidepressants

Tricyclic antidepressants have been found to have numerous in vivo and in vitro effects on central neurotransmitters, including block of amine uptake and decrease in sensitivity of presynaptic (and postsynaptic) α_2-adrenergic receptors and in sensitivity of β-adrenergic receptors (69). In a placebo-controlled study of anorectic patients, clomipramine was not associated with greater weight gain or improved eating behavior at 8-week, 1-year, and 4-year follow-ups (70), and amitriptyline failed to differ from placebo in the treatment of 25 anorectic patients (71). Double-blind, placebo-controlled studies in bulimic patients have shown that both imipramine (72) and desipramine (73) are significantly superior to placebo in reducing binge eating and purging behavior but that amitriptyline is not (74).

Newer antidepressants have variable effects on neurotransmission: nomifensine is a potent blocker of nor-

TABLE 1. Summary of Animal Studies on the Effects of Neurotransmitter and Neuromodulator Administration on Feeding Behavior

Item	Findings	Implications
Neurotransmitter system		
Noradrenergic and adrenergic	Application of α_2-adrenergic receptor agonist to the paraventricular nucleus produces hyperphagia; application of β-adrenergic receptor agonist to the perifornical region of the hypothalamus inhibits feeding (4, 5)	Stimulates or inhibits feeding, depending on the area of the brain
Serotonergic	Serotonin inhibits feeding by acting on the ventromedial hypothalamus (27)	Inhibits feeding
Dopaminergic	Central administration of low doses of dopamine stimulates but high doses inhibit feeding by acting on the perifornical hypothalamus (3, 37)	Stimulates or inhibits feeding, depending on the amount of neurotransmitter
Opioid	Administration of opioid antagonist (naloxone) decreases feeding following food deprivation (39)	Stimulates feeding
	Central administration of κ-opioid agonists enhances feeding (37)	Stimulates feeding
Neuromodulators		
CRH	Central administration reduces starvation-induced feeding (42)	Inhibits feeding
Cholecystokinin	Systemic administration inhibits feeding (55, 58, 59)	Inhibits feeding

epinephrine uptake and has some effect on the uptake of dopamine; bupropion may be metabolized to amphetamines and also has some effect on uptake of dopamine; fluoxetine seems to be a relatively selective blocker of uptake of serotonin; and trazodone seems to have some serotonin-uptake-blocking effect (69). The only controlled study on the effects of one of these newer antidepressants in the treatment of bulimia (75) showed that bupropion had a greater effect than placebo. Uncontrolled trials suggested the efficacy of nomifensine (76), fluoxetine (77), and trazodone (78).

Some putative antidepressants (mianserin and cyproheptadine) have serotonin-receptor-blocking effects, although mianserin also appears to block the uptake of norepinephrine (69). A double-blind study of 72 patients with anorexia nervosa (79) showed that cyproheptadine had a marginal effect on decreasing the number of days necessary to achieve a normal weight but increased treatment efficacy significantly in the nonbulimic subgroup of these patients when compared with amitriptyline and placebo. Mianserin did not prove superior to placebo in reducing bulimic symptoms in a controlled trial on patients with bulimia nervosa (80), although the dose used was only 60 mg/day, which may be low.

MAOIs are antidepressant agents that inhibit an enzyme important for the inactivation of endogenous monoamines. No controlled studies have been reported on the use of these antidepressants in the treatment of anorexia nervosa. In an open study of only six anorectic patients (81), treatment with isocarboxazid was associated with partial improvement in eating behavior. In bulimia nervosa, phenelzine was significantly superior to placebo in a double-blind trial with 50 women (82), and isocarboxazid appeared to be more helpful on most eating behavior measures than placebo in a double-blind study of 24 bulimic patients (83).

Lithium can inhibit the release of norepinephrine and dopamine and can increase the release of serotonin. A placebo-controlled trial with anorectic patients (84) showed that lithium may augment weight gain in patients treated with behavioral modification, but the results were not clinically meaningful. Preliminary findings on 13 patients with bulimia nervosa participating in an 8-week, double-blind, placebo-controlled trial of lithium (85) showed no difference between lithium and placebo.

Other Drugs

Oral naltrexone, a long-acting opiate antagonist, appeared to have a positive effect in six of eight patients in an uncontrolled trial (86). In a 6-week controlled study of 16 subjects with bulimia nervosa (87), high-dose oral naltrexone induced a significant reduction in frequency of binge eating or purging and low-dose oral naltrexone had no significant effects on these behaviors.

Fenfluramine, a sympathomimetic amine that increases central serotonin turnover, appeared to be effective in treating bulimia nervosa in a controlled study with desipramine (88).

L-Tryptophan, which is a serotonin precursor, did not appear to be effective in treating bulimia in a double-blind, placebo-controlled trial (89).

Clonidine, a preferential α_2-adrenergic receptor agonist, had no effect on eating behavior in a double-blind, placebo-controlled trial (90).

DISCUSSION

Table 1 summarizes the results of animal studies on the effects of neurotransmitters and neuromodulators on feeding behavior. Tables 2 and 3 summarize the results of studies on neurochemical abnormalities in anorexia nervosa and bulimia nervosa, respectively.

Anorexia nervosa seems to be associated consistently with lower concentrations of norepinephrine

TABLE 2. Summary of Studies on the Neurochemical Abnormalities in Anorexia Nervosa

Item	Findings	Implications
Neurotransmitter system		
Noradrenergic and adrenergic	Lower norepinephrine and MHPG in plasma, urine, and CSF (2, 12–19)	Less norepinephrine turnover
	Greater number of platelet α_2-adrenergic receptor binding sites (17, 22, 23)	Less norepinephrine activity
Serotonergic	Normal CSF 5-HIAA (21)	Normal serotonin turnover
	Lower CSF 5-HIAA (20)	Less serotonin turnover
Dopaminergic	Normal CSF HVA (19, 21)	Normal dopamine turnover
	Lower CSF HVA (20)	Less dopamine turnover
Opioid	Greater CSF total opioid activity measured by radioreceptor assay (43)	Greater opioid activity
	Normal CSF β-endorphin in extremely underweight patients (42)	Normal β-endorphin turnover
	Reduced CSF β-endorphin in extremely underweight patients (44)	Less β-endorphin turnover
Neuromodulators		
CRH	Higher CSF levels of immunoreactive CRH (49, 50)	Greater turnover
Vasopressin	Subnormal or erratic response to hypertonic saline (54)	Dysregulation in secretion

TABLE 3. Summary of Studies on the Neurochemical Abnormalities in Bulimia Nervosa

Item	Findings	Implications
Neurotransmitter system		
Noradrenergic and adrenergic	Higher number of platelet α_2-adrenergic receptor binding sites (22)	Less norepinephrine activity
	Reduced resting levels of plasma norepinephrine and blunting in the rise of plasma norepinephrine on standing (24, 25)	Less norepinephrine turnover
Serotonergic	Smaller probenecid-induced increases of CSF 5-HIAA in weight-restored bulimic anorectic patients than in nonbulimic anorectic patients (36)	Less serotonin turnover
	Absent rise in plasma L-tryptophan-large neutral amino acids in bulimic patients who did not feel satiated after a binge (34)	Less serotonin turnover
Neuromodulator		
Cholecystokinin	Reduced total integrated plasma response to eating and peak plasma response after eating (60)	Impaired secretion in response to a meal

and MHPG in the CSF and with a higher platelet α_2-adrenergic receptor number and greater sensitivity, suggesting a reduced norepinephrine activity and turnover. The findings of the studies on serotonergic and dopaminergic activity in patients with anorexia nervosa are variable. Patients with anorexia nervosa also seem to have elevated CSF total opioid activity and elevated CSF levels of CRH, together with abnormalities in the secretion of vasopressin.

Bulimia nervosa is accompanied by lower than normal peripheral and, perhaps, central noradrenergic function with more than the usual number of platelet α_2-adrenergic receptor binding sites. Less serotonergic activity in bulimia nervosa is suggested by the finding that weight-restored anorectic patients with bulimia have lower probenecid-induced CSF levels of the serotonin metabolite 5-HIAA than weight-restored nonbulimic anorectic patients. Finally, patients with bulimia nervosa seem to have an impaired secretion of cholecystokinin in response to a meal.

These neurochemical abnormalities could have implications in the psychopharmacological approach to the treatment of eating disorders. In fact, psychotropic drugs are known to affect various neurotransmitter and neuromodulator systems and, although no drug has been consistently effective in the treatment of anorexia nervosa, numerous psychotropic drugs (particularly tricyclic antidepressants and MAOIs) appear to be promising agents in the treatment of bulimia nervosa.

It appears that patients with abnormal eating behavior have important changes in CNS neurotransmitter and neuromodulator systems that are known to modulate hypothalamic-pituitary function and may therefore underlie such physical manifestations of eating disorders as osteoporosis, infertility, and amenorrhea that are intimately connected with the neuroendocrine apparatus (91).

Changes in hypothalamic-pituitary function may be secondary to the patient's dieting and caloric deprivation. Studies indicate that refeeding and weight gain ameliorate these neuroendocrine changes, suggesting that they are secondary either to weight loss or to caloric deprivation (92). A longitudinal study of 24 inpatients with anorexia nervosa demonstrated a normalization of all the neuroendocrine abnormalities (higher cortisol secretion, cortisol nonsuppression in response to dexamethasone, and abnormal 24-hour plasma luteinizing hormone pattern) after 10% weight gain (93). The authors concluded that the dysfunctions in the hypothalamic-pituitary-adrenal/gonadal axes of these patients have little specificity for this disease and are mainly a consequence of nutritional factors and starvation (93). However, it is also possible that certain neuroendocrine abnormalities may be secondary to abnormal eating behaviors such as intermittent starvation or marked fluctuation in food intake.

Even if we assume that the neurochemical and neuroendocrine changes associated with eating disorders are secondary to dieting and caloric deprivation, it is possible that these changes may in turn perpetuate the pathological behavior and be responsible for a number of psychiatric symptoms (94). In one study (95), voluntarily starving subjects manifested many psychological symptoms seen in anorexia nervosa, including disturbed mood and altered eating behavior. In 64 patients with anorexia nervosa, body weight and β-hydroxybutyric acid, a good indicator of caloric restriction, were significantly correlated with mood and neurovegetative aspects of depression when the effects of diagnostic group and specific psychopathology were controlled (96). These findings suggest that at least some depressive symptoms in eating disorders are related to low body weight, dieting, and starvation. Animal experiments have shown that starvation causes a decrease in noradrenaline turnover in the CNS of the rat (97), and changes in central noradrenergic metabolism have been implicated in depression (7).

Finally, it has been postulated that CNS changes may precede the onset of abnormal eating behavior (98), and the neurochemical abnormalities observed in the patient with an eating disorder may therefore be primary.

It is apparent that further research on the neurochemistry of eating disorders is crucial to the understanding of the pathophysiology of these disorders and to the development of more effective pharmacological and cognitive-behavioral treatments.

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Psychiatric Aspects of Organ Transplantation

Owen S. Surman, M.D., C.M.

Technical advances in surgery and the new antirejection agents cyclosporine and muromonab-CD3 have led to improved outcome for organ transplantation. Allograft rejection and complications of immunosuppressant therapy are often associated with considerable stress, so availability of psychiatric consultation is a necessity. As a transplant team consultant, the psychiatrist treats perioperative anxiety, depression, and organic brain dysfunction and addresses medical and ethical aspects of patient selection. Studies indicate that many patients with psychopathological conditions have good postoperative results and that most living kidney donors participate spontaneously and consider donation a positive experience.

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Organ transplantation has met with increasing success and clinical application. Contributing to this success have been technological advancement and the introduction of new immunosuppressive agents: cyclosporine and muromonab-CD3. An eager response by the American public has overshadowed the reticence of insurers and the doubts of some health care policy planners.

SURVIVAL AND QUALITY OF LIFE

In the 1960s, transplantation of the liver, heart, or pancreas was principally a laboratory event. Renal transplantation gained clinical acceptance, backed by hemodialysis as alternative renal failure therapy. In 1972, the U.S. Congress enacted government sponsorship of end-stage renal disease therapy. Relatively poor results in transplantation of the liver and the heart led to surgical moratoria in the 1970s. Currently, about 75% of liver transplant recipients, 75%–80% of heart transplant recipients, and over 90% of kidney transplant recipients are alive at 1 year (1–5). Full rehabilitation occurs in two-thirds to four-fifths of those whose grafts are functioning at 1 year, as reported by clinicians at active transplant centers (6–9).

Evans et al. (10) studied 859 patients with end-stage renal disease and found that 79.1% of 144 kidney transplant recipients and 47.5%–59.1% of 715 dialysis patients were functioning at nearly normal levels. The standardized data obtained from the patients included the Karnofsky index of psychological affect, index of overall life satisfaction, and index of well-being. Uniform study procedures were used to collect medical data from the patients, physicians familiar with the patients' functional status, and medical records. In the past, 10% of patients with end-stage renal disease have been treated with transplantation, but Eggers (11) found that the trend is now toward increased use of transplantation, especially in the segment of the population under age 55, and that 32% of all Medicare beneficiaries with end-stage renal disease received transplant as of 1985.

A formal survey conducted in the United Kingdom by O'Brien et al. (4) demonstrated that 90%–92% of heart transplant recipients were free from quality of life restrictions, according to the Nottingham Health Profile, 3 months after their transplants. Comparable findings in the United States have been obtained with the Sickness Impact Profile (12) and other follow-up questionnaires (13). Interpretation of such findings must allow for the limits of patient reports (14).

In a preliminary report, Tarter et al. (15) discussed a series of life quality studies of a subset of liver transplant recipients. In one study using the Sickness Impact Profile and the Social Behavioral Assessment Schedule, there was a "substantial positive change" in social functioning from before surgery to 2 years after surgery. Of 66 transplant survivors given a social adjustment questionnaire 1 year after surgery, most were satisfied with the quality of their lives. However, they had not returned to their premorbid baseline and had significant residual impairments in some aspects of emotional, cognitive, and psychomotor function.

Now that transplantation of the kidney, liver, and heart are no longer experimental procedures, a new spectrum of organ transplants is at the borderline between experiment and clinical reality. Pancreas transplantation is an emerging technology. Cosimi et al. reported that 20 of 24 combined pancreas and kidney transplants were functioning 2 days to 2 years after

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transplant (16, personal communication). As of January 1989, 21 (84%) of 25 patients with pancreatic grafts were insulin free (A.B. Cosimi, personal communication). Despite normalization of glucose tolerance and absence of insulin requirements, diabetic patients with advanced complications continue to experience progression of retinopathy after receiving new pancreases (17). The current trend is toward early identification of patients with type 1 diabetes, who might be spared such secondary complications.

Combined heart and lung transplants are being performed in some centers, and there are also indications for transplantation of the lungs in some patients with primary lung disease (18, 19).

PSYCHIATRIC ASPECTS OF THE PRETRANSPLANT PERIOD

For many with organ failure, the pretransplant period is marked by declining physical function, adjustment-related anxiety and depression, and development of organic brain deficits.

Organic Brain Syndrome

There has been ample documentation of CNS dysfunction in uremic patients (20–26). Contributing factors include toxic metabolites, anemia, hypertension, endocrinopathy, and cardiovascular impairment. Special neurologic syndromes unique to the dialysis population are dialysis dysequilibrium and dialysis dementia (20, 25, 27–30). Seizures commonly occur in renal failure (20, 24, 25, 31–33). Complex partial seizures may be a cause of disruptive behavior; even catatonia may respond to anticonvulsant therapy (34).

Organic brain syndrome is commonly observed among liver transplant candidates and derives principally from intestinally absorbed toxic metabolites (hepatic encephalopathy) (35–38). Detection of organic brain syndrome is facilitated by EEG and trail-making tests (39). Trzepacz et al. (37) found a 30% prevalence of delirium, according to *DSM-III* criteria, among 40 patients awaiting liver transplantation. The measures used were the Mini-Mental State, trail-making tests, EEG, and serum albumin level. Surman et al. (8) reported preoperative evidence of organic brain syndrome, as determined with the Parsons-Smith et al. criteria (38), in 50% of 34 adult candidates for liver transplantation. In a recent study, Trzepacz et al. (40) diagnosed delirium in 18 (16.7%) of 108 liver transplant candidates. Delirious and nondelirious patients were distinguished with high specificity and sensitivity by means of the Trailmaking B Test, EEG, and serum albumin level.

Among candidates for heart transplantation, organic brain syndrome may result from CNS hypoperfusion. Pretransplant psychological assessment should allow for such metabolic stress and be followed by neurologic evaluation in the event of serious cognitive impairment (41, 42). Using the Mini-Mental State, Freeman et al. (43) found a 3% preoperative prevalence of organic brain syndrome, according to *DSM-III* criteria, among 70 heart transplant patients. Prevalence estimates for organic brain syndrome are likely to vary widely depending on inclusion criteria and means of assessment. Trzepacz et al. (40) noted that mild forms may fail to meet the *DSM-III* criteria, and the Mini-Mental State is less sensitive than EEG, or the Trailmaking B Test, or both.

Clinical evidence of organic brain syndrome is available through careful behavioral observation and inquiry. Forgetfulness and episodic confusion among encephalopathic patients may be revealed through patient interviews or discussion with family members and hospital nursing staff. Patients with organic brain syndrome often lack sufficient attentiveness to complete customary tasks, such as television program viewing and routine reading. In our center we have relied on careful history taking, mental status testing, and physical examination (e.g., to demonstrate asterxis) for diagnosis of organic brain syndrome. However, the research value of standardized testing is compelling.

Patient Morbidity

While the patient with end-stage renal disease has recourse to dialysis, conservative medical supports are the only option for patients with end-stage heart and liver disease. Many such patients are critically ill at the time of transplant evaluation or decline in health while they wait for donor organs. Surman et al. (8) reported stupor in six of 40 liver transplant candidates. One family was making funeral preparations when their relative was placed on the list for a donor organ.

Christopherson (44) reported on the challenge to heart transplant candidates, whose families must simultaneously prepare for death and survival. "Spouses often intersperse talk about funeral arrangements with plans for a family vacation after the patient comes home." One 21-year-old cardiomyopathy patient received a cadaveric heart after he had been in the coronary care unit for 5 weeks with an intra-aortic balloon pump. Such levels of morbidity are common among cardiac transplant candidates (W. Dec, A.M. Reither, personal communications). Approximately 20% of heart transplant candidates die while waiting for donor organs, and this percentage is likely to increase because donor supply is markedly exceeded by potential recipients (W. Dec, personal communication).

Preoperative Adjustment

Psychological effects of organ failure are best known in the setting of end-stage renal disease. Body image impairment and depression were observed among hemodialysis patients by early investigators (45–48). Abram (49) estimated the incidence of suicide to be 100 to 400 times greater than in the general population. More recently, Neu and Kjellstrand (50) reported that suicide occurs among dialysands at a rate 15 times that of the general population. Sexual dysfunction among renal failure patients has been found to be related to endocrine and other metabolic factors (47, 51–53).

Cassileth et al. (54) compared six patient groups and found that the adjustment of patients with chronic renal failure is comparable to that of patients with other chronic diseases. Kaplan De Nour and Czaczkes (55) found that renal failure patients who deal best with anger and dependency have the most favorable outcome. Denial as a defense has been prominent in the hemodialysis population (26, 49, 53, 56–60) and has been reported by Mai et al. (61) among heart transplant recipients.

Family and marital stress is evident among patients with organ failure. In an early study by Short and Wilson (59), family concern about survival led patients to increasingly become spectators in their homes. Others (26, 44, 62) have reported a change in spousal role to nurse and medical caretaker. Christopherson (44) found that almost all spouses who had recently married heart transplant patients "make at least one reference to the 'person I might have married instead.' " Tarter et al. (15) found spousal distress to be highly correlated with the emotional and somatic impairment experienced by liver transplant patients.

Adjustment disorders are prevalent in transplant candidates (8, 35, 43, 63, 64). House et al. (35) performed psychiatric evaluations and chart reviews for 34 liver transplant candidates. Among adults, organic brain syndrome and depression were prevalent; among children, anxiety, regression, and family stress were evident. Psychiatric symptoms were found in half of the children and all but one adult. Mai et al. (42) used a modified form of the Present State Examination and identified anxiety and/or depression in 34 of 66 patients assessed for heart transplantation. Kemph (65) noted phobic anxiety among some patients with renal failure. Kahn et al. (66) identified panic disorder in 29 of 35 heart transplant candidates with cardiomyopathy. A history of alcohol abuse was present in 25% of the sample.

In general, psychiatric symptoms in transplant patients and their families are related to level of comorbidity from organ failure and availability of successful medical and surgical interventions. One should remain alert to instances in which a past history of substance abuse contributes to the pathogenesis of end organ disease. I recently encountered a 42-year-old heart transplant candidate whose cardiomyopathy improved dramatically with the diagnosis and treatment of her alcoholism.

Preoperative Treatment

Medical intervention is of primary importance in managing organic brain syndrome and psychological stress among those awaiting transplant (26, 42, 53). Patients with renal failure who tolerate hemodialysis poorly may benefit from continuous abdominal peritoneal dialysis. Hepatic encephalopathy is managed by clearing toxic metabolites from the bowel with lactulose and by controlling sepsis and bleeding. Among those with end-stage heart disease, CNS function is aided by antiarrhythmia therapy and circulatory support.

The need for supportive psychiatric care and social service intervention for pretransplant patients with end organ disease is self-evident. Mumford et al. (67) reviewed studies of preoperative psychiatric intervention among surgical patients. The studies suffered methodologically from an absence of blind ratings but indicated that the patients who received psychiatric intervention spent less time in the hospital than control subjects. Thorough preoperative teaching by the nursing staff is an established method of decreasing preoperative stress among patients undergoing cardiac surgery (68, 69). The extended work-up and wait preceding transplant provide an opportunity for bonding between the patient and surgical team (8). Social services have been widely used to provide emotional support for patients and their families, financial evaluation, and assistance with living arrangements (8, 70). Some patients benefit from meetings with successful allograft recipients and from participation in patient-centered organizations. Family discussions help foster a realistic understanding of the patient's illness (71).

Preoperative antianxiety and antidepressant pharmacotherapy and substance abuse counseling should be available (68). Watts et al. (63) suggested that depression can be identified by the presence of suicidal thinking, constricted affect, and feelings of worthlessness. Antidepressant medication is often well tolerated by renal failure patients. They generally require lower doses than the medically healthy (53). Some cardiac patients with depression respond well to alprazolam (63, 72). Imipramine, doxepin, and nortriptyline have shown no adverse effects on left ventricular function (72–74). For patients with heart failure, antidepressants can be used if consideration is given to other potential side effects, such as tachycardia, increased conduction time, and orthostasis. Cassem (72) has advised a "start low, go slow" approach.

The majority of psychotropic agents are hepatically metabolized, and caution is indicated in hepatic failure. Oxazepam is preferred among antianxiety agents because of the relative ease of hepatic degradation, and diphenhydramine is frequently effective as a hypnotic sedative (8). If antidepressants are prescribed for a patient with hepatic dysfunction, it is essential to measure medication blood levels frequently and to be aware of a possible reduction of the seizure threshold.

Kahn et al. (66) successfully treated panic disorder with alprazolam in 10 patients with cardiomyopathy. Phobic desensitization has been used with patients who experience preoperative anxiety (68). Surman and Tolkoff-Rubin (75) used hypnosis to maximize perceived control among hemodialysis patients. Self-hypnosis and associated cognitive strategies should be available preoperatively for those who are motivated and in need (8, 53, 68).

To establish rapport with patients and their families, the consulting psychiatrist must acknowledge the stress experienced by transplant candidates and the extent to which organ failure impedes coping skills. The next step is to identify specific psychiatric syndromes and to implement appropriate psychotherapeutic, psychopharmacologic, and/or psychosocial intervention. In doing so, the consultant should appreciate the limitations of *DSM-III-R* as applied to the medically ill. Psychological factors that could impede successful surgical outcome should be identified and candidly reviewed with the transplant team along with strategies that may reduce the potential for postoperative psychiatric complications.

SELECTION OF TRANSPLANT CANDIDATES

Selection for end-stage renal disease therapy in the mid-1960s was a case of "lifeboat ethics." Selection committees came to be known as "God squads." Through passage of Public Law 92-603 in 1972, Congress made funds available for renal failure victims. What Fox and Swazey (76) referred to as the "gatekeeper" function of medicine passed to the federal government for this type of catastrophic illness. Physician denial of treatment came to be seen as morally unjustified.

The current success of organ transplantation once again highlights discrepancies between supply and demand. Hearts are especially scarce. Schroeder and Hunt (5) estimated that over 1,000 heart transplants were performed in 1987 and that only one-tenth of the projected number of hearts needed are available. The current yearly demands for kidneys and livers are, respectively, 65 and 40 per million population. The actual rates of kidney and liver transplants are 40 and 5 per million (A.B. Cosimi, personal communication).

The increased success of transplantation also casts a spotlight on the relatively few instances in which graft failure follows from patient noncompliance with immunosuppressant treatment. Armstrong et al. (77) identified only 11 such cases of graft loss in 460 kidney transplant patients. Our experience with approximately 1,000 cases is similar. Didlake et al. (78) reported a 4.7% incidence of late graft loss from noncompliance among 531 kidney transplant recipients.

With society increasingly focused on medical care costs, the survival statistics of active transplant centers will have to achieve state-of-the-art success rates to maintain federal licensure. The United Network of Organ Sharing is an indirect product of the National Transplant Act of 1984 and is administered under the Health Resources and Service Administration. According to its standards, transplant centers are subject to review if their survival rates for liver, pancreas, kidney, and heart transplants are in the lowest 5%. Full approval as a heart transplant center requires 12 cases per year and a minimum survival rate of 73% at 1 year and 65% at 2 years (F. Delmonico, personal communication).

These factors affect selection policy, which varies among transplant centers. Large, experienced centers with good results are likely to have a greater tolerance for high-risk patients and to accept motivated patients who go outside their own regions.

One objective of psychiatric screening has been to exclude potentially noncompliant patients. Psychiatric reports on selection have principally involved subjects requesting heart transplants. Factors typically mentioned as indicating unsuitability are substance abuse and past medical noncompliance (5). McAleer et al. (70) reported that six of 11 corresponding heart transplant centers used psychiatric criteria for determining which patients would not receive transplants.

Frierson and Lippmann (79) reported that 13 of 70 patients evaluated for heart transplantation were rejected for psychiatric reasons. After substance abuse, antisocial personality and impaired intellectual function were the most frequent diagnoses among rejected patients. In the same series, four of 17 patients with preoperative psychiatric disorders who did receive transplants exhibited significant postoperative noncompliance. This result can be interpreted to mean that many transplant patients with preoperative psychiatric disorders are capable of successful postoperative outcome. That has been the experience at our center.

While great caution must be exercised in excluding patients because of psychiatric findings, psychiatric diagnosis is a preoperative risk factor. Freeman et al. (43) reported less satisfactory outcome among patients undergoing cardiac transplant who met *DSM-III* criteria for psychiatric disorders. Nineteen of 70 patients received the preoperative designation "reservation about suitability for transplantation." Fourteen of the 19 so designated had postoperative surgical or psychiatric complications. Cooper et al. (41) cited noncompliance as a major factor in seven of 27 deaths in a series of 39 heart transplants. The authors found that age under 40, cardiomyopathy, unstable job history, unmarried status, and medical care outside of the transplant location were factors in failures of compliance. Exclusion on psychiatric grounds was nonetheless advocated in only extreme circumstances. Mai et al. (42) have also advised caution about excluding patients on the basis of psychiatric criteria, except in instances of recent alcoholism or drug abuse. Didlake et al. (78) pointed to a lack of "valid and reliable indicators" for graft loss secondary to noncompliance. They recommended psychiatric intervention "rather than inappropriate denial of transplantation to those who can benefit medically."

For liver and heart transplant candidates with alcoholism, a 1-year period of abstinence has been required at our center. This is a modification of the 2-year abstinence period initially required by the Boston Center for Liver Transplantation (8, 80).

Alcoholism is the leading cause of liver disease. It is also a frequent finding among patients with idiopathic cardiomyopathy (44, 66). Recent alcoholism may add to the morbidity of transplantation by impairing nutritional status and contributing to other end organ effects. The potential for debilitating postoperative psychopathology and recurrent drinking is evident in the experience of Dubovsky et al. (81), who described a 38-year-old man whose liver transplant was complicated by delayed wound closure. Postoperative noncompliance has led in the past to relatively poor 1-year and 3-year survival statistics for alcoholic patients (7).

More recently, however, Starzl et al. (82) reported a 73.2% 1-year survival rate for 41 patients who received liver transplants for alcoholic cirrhosis between 1980 and 1987. Alcohol abuse reportedly was rare among those who survived longer than 6 months. Our group is currently assessing the feasibility of liver transplantation for well-motivated alcoholic patients with less than 1 year of established sobriety.

It is difficult to predict the occurrence of posttransplant graft loss due to poor medical compliance, and it is of singular importance that consultants recognize the limits of their expertise. Faced with terminal illness, patients' patterns of motivation may change. Also, diagnosis of psychiatric disorder is sometimes difficult in the setting of somatic illness (42, 63, 83). Unexpected situational factors frequently play a role in outcome. Armstrong et al. (77) noted that only one of 11 noncompliant kidney transplant patients met research diagnostic criteria for psychiatric disorders. Those authors emphasized that graft loss due to noncompliance is an uncommon outcome and therefore unlikely to be significantly affected by selection procedures. In a retrospective review of 408 transplant patients, substance abuse, depression, and age less than 31 years were found to be typical of seven patients (1.7%) who lost kidney allografts because of noncompliance (D.R. Gastfriend, O.S. Surman, unpublished data). Many patients who were continuing substance abusers were, however, able to maintain good allograft function.

One must ensure that pretransplant evaluation does not become a setting for social judgment. Merrican and Overcast (84) wrote that stringent selection may constitute a breech of federal laws related to the handicapped. Loewy (85) cautioned that the physician-patient relationship is an inappropriate setting for the application of social worth criteria, however germane the latter may be to "macroallocation" of scarce resources. Rejection on a sociological basis should be rare, although "informal screening" does occur among referring physicians.

In my experience, kidney transplantation has proven possible in patients with a variety of psychopathological conditions. Two kidney allograft recipients had full-scale IQs of 50. Others have had documented personality disorders (26). Several have had borderline intellectual function, past history of affective disorder, or past alcohol and/or substance abuse (26, 53). One patient with borderline personality and a history of graft loss due to noncompliance was medically unstable while receiving long-term hemodialysis. Retransplantation with a cadaver kidney followed total lymphatic irradiation for immunosuppression. The patient has maintained long-term allograft functioning despite continued psychosocial turmoil and substance abuse.

Many patients with especially good outcomes have sustaining spiritual lives or are motivated by plans for the future (8, 86). A challenge for transplantation psychiatrists is to establish preoperative psychosocial and medical interventions that will maximize the chances of favorable outcomes for those with psychiatric vulnerability.

DONOR PARTICIPATION

The primary source of donor organs is cadavers, but only 15% of potential donors contribute (87). Of the families that do participate, the majority find it a positive aspect of losing their loved ones (88, 89). The motivation may be altruism, the deceased family member's previously expressed wishes, or family medical history (90). Youngner et al. (91) discussed the impact of organ retrieval on hospital personnel.

The need for improved organ availability is a societal challenge. Some countries presume post-mortem consent but allow families to opt out of donating cadaveric organs (88, 92–94). Caplan's advocacy of "required request" (95) has led to state laws requiring hospital personnel to ask relatives of the deceased for donor organs. The commercial marketing of organs has been suggested by some but was specifically outlawed by the National Organ Transplant Act (88). Other forms of financial incentive might include tax benefits for those who make commitments to cadaveric donation while living (94). Miller (88) has suggested "mandatory consent," whereby adults would be required to consent or object in writing to post-mortem organ donation.

Participation of living related donors in kidney transplantation is widely accepted and supported by U.S. law for consenting adults and assenting minors. The basis for these rulings has been the expected emotional benefit to the donor (49, 53, 96). The advantages to the recipient of receiving a kidney from a living relative are enhanced allograft compatibility and a reduction in postoperative immunosuppression. The increasing acceptance of nonrelated donors results from the long wait for cadaveric kidneys, from improved organ quality, and from the potential value of donor-specific transfusion and preoperative immunosuppression (87, 97–100). Some have found it acceptable to use partial pancreas transplants from living donors (101).

Death of a living donor is rare, and the estimated risk of death from donation has been equated to the risk from commuting about 16 miles a day (102), i.e., 0.03%–0.09% (87, 102–104). Serious treatable complications occur in 2%–3% of the cases (87). It is interesting that evaluation of donors occasionally results in discovery of a previously undetected lesion and subsequent life-saving treatment.

Among the psychiatrists expressing concern about donor altruism were Kemph, who described postoperative depression and resentment among donors (49, 65), Bieber, who referred to "neurotic motives" (49), and Crammond, who observed donor-recipient conflict and insufficient donor recall of preoperative interview data (64, 105). Abram (49, 106) discussed early views of donor altruism versus neuroticism and made a literary reference to the fabled attempt of Tolstoy's Grushenka to reach salvation through her one charitable gift of an onion. The principal ethical question among those who doubted donor altruism was whether donors are coerced. Opinion varied as to whether preoperative psychiatric evaluation of potential donors should be mandatory or optional. In the event that the donor was considered psychiatrically inappropriate, biologic incompatibility was frequently cited as the contraindication (26, 49, 76), a practice I find unjustifiable. Patients and their potential donors have a right to be informed of the facts. A donor candidate who is rejected for psychiatric reasons may choose to obtain an opinion from another transplant group or may become acceptable later. For example, in our center we recently accepted a donor with a 10-month history of abstinence from alcoholism. The same individual had been previously rejected by our group because of active drinking.

The weight of evidence indicates that kidney donation has favorable outcomes for donor and recipient. Fellner and Marshall (107, 108) studied 12 kidney donors and described the spontaneity of their participation and their persisting positive regard for the experience. Eisendrath et al. (49, 109) studied 25 donors, most of whom felt they had been "called." Sadler et al. (110) interviewed 18 genetically unrelated donors and found a postoperative improvement in self-esteem among all participants, nine of whom had had only transient prior relationships with the recipients. Cain et al. obtained reports of improved donor-recipient relations from a majority of 70 donors (L. Cain, personal communication), and Simmons et al. (99, 111–113) described improved self-esteem and favorable long-term adjustment in a series of studies of related donors. In a telephone questionnaire study of 536 donors from five centers, Smith et al. (114) found that 97% reaffirmed their decisions and less than 15% said they had felt pressured to donate or to abstain. Sharma and Enoch (115) used the Present State Examination in a 5–10-year comparative study of 14 donors and nine candidates who were ruled out for medical reasons. The authors found no adverse psychological effects from organ donorship.

A series of surveys by interview or questionnaire has demonstrated positive lay attitudes about transplantation (99, 116–118). Improving postoperative results and a favorable societal response may provide reinforcement for those who choose to donate organs. Some transplant surgeons, most notably Thomas Starzl, prefer to avoid the discomfort and risk of donor surgery (debate with E. Friedman, Fifth International Conference on Psychonephrology, New York, October 1986). As one team wrote, "Obtaining an organ without putting a live donor at jeopardy is irresistible in the long view" (119).

The care of a living donor is facilitated when an evaluating physician acts as health care advocate (53, 120). An ambivalent donor typically resolves the situation by not following through with planned studies (121). Psychiatric intervention is advisable when a motivated donor experiences family conflict about elective surgery, when there is significant history or current clinical evidence of psychiatric impairment, or for amelioration of preoperative anxiety (53).

POSTOPERATIVE PSYCHIATRIC DISORDERS

Up to a week of intensive care is commonly required by recipients of heart and liver transplants, while those receiving new kidneys typically enjoy a more rapid return of health. In our institution, the average period of hospitalization after liver transplantation is 25–30 days, and for kidney transplantation it is 9–11 days (P.S. Russell, personal communication). The promise of extended life and healthful changes in appearance promote feelings of rebirth. Changes in body image or identity may derive from the marvel of renewed physiological functioning. Castelnuovo-Tedesco (122) wrote that the graft is not psychologically inert and that the recipient develops a prominent identification with the donor. A remarkable example is Abram's account of the Ku Klux Klan Grand Dragon who joined the National Association for the Advancement of Colored People after learning that his new kidney came from the cadaver of a black person (49). A liver transplant recipient thought transiently of her new organ as "the little girl I never had" (8). A few transplant recipients have experienced impairment of gender identity (64, 81, 122). Such events may be a manifestation of organic brain dysfunction.

Organic Brain Syndrome

Improvement in CNS function is an expected outcome of transplantation. Tarter et al. (123) documented postoperative reversal of hepatic encephalopathy among 10 liver transplant patients whom the authors compared to 10 patients with Crohn's disease.

Postoperative organic brain syndrome is typically a manifestation of metabolic impairment and is more commonly seen among liver and heart recipients in the early postoperative period. Hotson and Enzmann (124) stated that organic brain syndrome accompanied by psychosis in the first 48 hours after heart transplantation is probably the result of intraoperative ischemia. The themes of such delirious thoughts may be memorable; one heart transplant recipient "dreamed" that he and a transplant nurse were attempting "to stop Santa Claus from taking over the world." Organic brain syndrome among kidney allograft recipients was more frequent in the 1960s and 1970s, when patients required sustained treatment with high doses of corticosteroids (125). Transient disruption of sleep, altered perception, and lability of mood often occur among those receiving "pulses" of corticosteroids as antirejection therapy. Cyclosporine is an important antirejection drug with potential adverse effects on the kidneys, liver, and CNS. It should be considered in the etiology of organic brain syndrome, tremor, seizures, or otherwise unexplained neurotoxicity. Reports of cyclosporine toxicity have most often involved liver transplant recipients (126–129). De Groen et al. (130) postulated that adverse CNS effects of cyclosporine are more likely when there has been prior disruption of the blood-brain barrier, as might occur in patients with histories of hepatic encephalopathy. De Groen et al. (128) also described a "syndrome of encephalopathy, seizures and white-matter changes" with varying CNS manifestations and associated with a low serum total cholesterol level. In three patients with cerebral manifestations, including cortical blindness, quadriplegia, confusion, and coma, the toxicity was reversed with dose reduction or discontinuation of cyclosporine. Boon et al. (131) implicated cyclosporine in the cases of two patients with posterior cerebral lesions after liver transplantation. Both patients had very high cyclosporine levels, did not respond to dose reduction, and at post-mortem examination had predominantly white matter lesions with reactive astrocytosis in the occipital lobe. In the series by Vogt et al. (129), two patients developed multiple seizures and a cerebellar syndrome. Both patients improved, but in only one case was cyclosporine treatment discontinued. The authors were unable to conclude what role was played by cyclosporine. They pointed out that cyclosporine neurotoxicity has no clear relationship to cyclosporine blood level. While the role of cyclosporine in adverse CNS effects requires more study, Simmons and Abbress (132) found that the quality of life in 51 kidney transplant patients who received immunosuppression with cyclosporine and prednisone compared favorably with that of 40 patients who received antilymphocyte globulin, azathropine, and prednisone. Patients treated with cyclosporine did better on Campbell's well-being indexes and on other measures of physical and social well-being. A lower rate of infection and rejection explained the variance.

Postoperative Adjustment

Rejection is experienced at some point by most allograft recipients. The liver may be especially vulnerable in this regard (133). Rejection after heart transplantation is common and life-threatening. Repeated endocardial biopsy provides a clue to early rejection and is currently standard practice among heart transplant centers. The procedure is relatively painless. Since there is no nerve supply to the transplanted heart, discomfort is confined to the site where the biopsy instrument is inserted into the right side of the neck. Cardiac transplantation is also followed by normalization of sympathetic nervous system functioning through relief of congestive heart failure (134).

Anticipatory anxiety may precede the first rejection experience. It may be more prominent among those whose relatives or friends experienced adverse outcomes in similar medical situations. Once the routine for antirejection therapy is mastered, allograft recipients are generally more at ease. Anxiety is not uncommon before hospital discharge and often, in our experience, resolves with one or more successful outpatient visits. It is especially important for the transplantation psychiatrist to be vigilant about anxiety deriving from an undiagnosed medical complication. The best tool is a careful history of the presenting complaint and close collaboration with surgical colleagues.

Allograft rejection is often accompanied by withdrawal, depression, and reactivation of feelings associated with previous health impairment. Such adjustment disorders characteristically respond to successful antirejection management. Corticosteroids may be responsible for mood change and irritability that is less apparent to the patient than to others in the same environment. Changes in limbic excitation may play a role in steroid side effects (34, 135).

Infection is an important complication of transplantation and must be considered in the differential diagnosis of mental status alteration (26, 53). Infection is a common cause of depression in the posttransplant period. Depression is especially prevalent among patients with cytomegalovirus infection and may occur with a cytomegalovirus mononucleosis syndrome (53, 136).

Depression may result from unfulfilled expectations (125). Even a good medical outcome may be overshadowed by interpersonal loss. For example, a patient with successful pancreas and kidney transplants developed major depression when unable to share his medical victory with his ex-wife. Another recipient held unrealistic hopes for a return of her vision and was depressed despite normalization of her renal and pancreatic endocrine function.

For the majority of transplant recipients, life extension is accompanied by improved quality of family life, work, and recreational activity. In one series of kidney transplant recipients (26, 137), 84% experienced a return of sexual functioning to pre-illness levels. Weil et al. (138) studied 61 children of kidney transplant recipients for up to 16 years and found normal patterns of growth and development.

Medical dependency is not eliminated with transplantation, and uncertainty is engendered by the risk of recurrent rejection or complications of antirejection medication (26). The cost of cyclosporine, typically $5,000 annually at full dosage, is an added source of stress (53, 139).

At some time after transplantation, almost all patients experience a degree of anxiety and depression (64, 125, 140). Transplantation psychiatrists find that a well-functioning transplanted organ produces parallel improvement in the emotional well-being of the recipient (26, 49, 64, 141).

Some have suggested the possibility of psychologically induced rejection (122). Viederman (142) postulated that some instances of graft rejection represented failure to integrate a hostile introject. In another case he described allograft loss precipitated by reactivation of a latent conflict (120, 143). There has been no scientific validation of such a hypothesis. However, there are instances of medical noncompliance which might derive from impaired psychodynamics.

Noncompliance with antirejection medication may occur in major depression, in organic brain dysfunction, with substance abuse, or as part of an adjustment reaction, especially in the adolescent population. Such instances are difficult to predict. For example, a previously well-adjusted kidney transplant recipient became dependent on cocaine and stopped taking his medication when he was unable to find a suitable job with which to support his wife and children.

Postoperative Treatment

Having met the prospective transplant patient before surgery, the consultation psychiatrist is especially well placed to provide postoperative supportive intervention in periods of family stress or medical crisis (26, 53). Kemph (140) advised that an allograft recipient be helped to express guilt about the donor. In our center we avoid probing for such material but find it useful at times to teach recipients about the positive aspects of organ donorship. Buchanan (144) emphasized the need for an active therapeutic style. Cognitive behavioral intervention and other relaxation techniques may foster an enhanced perception of control among anxious patients.

Antianxiety agents should be used with attention to excessive sedation (120), especially in cases of hepatic dysfunction. Adjustment-related depression is often best treated supportively. When symptoms persist for more than a few days, treatment with antidepressants should begin, with the aforementioned caveats. We have preferred doxepin for patients experiencing sleep impairment and desipramine when lethargy is more prominent. These choices have not, however, been made on the basis of systematic comparison. One must be mindful of a possible reduction in seizure threshold with antidepressants, and in cases of hepatic dysfunction one should be cautious about the long half-life of fluoxetine.

Postoperative organic brain syndrome generally responds to medical intervention or adjustment of antirejection medication. A relative or close friend at the bedside may obviate the need for neuroleptics. In over a decade of experience, we have rarely found aggressive doses of antipsychotic medication to be required. Low doses of intravenous haloperidol (up to 5 mg/day) have been helpful for agitation in three of our 17 heart transplant recipients. Mai et al. (42) were similarly conservative in approach and used antipsychotic agents in 10% of their patients. A discussion of delirium following cardiac surgery has been presented elsewhere (68, 69, 124).

Complex partial seizures should be considered in the etiology of persisting organic brain syndrome and may be effectively treated with carbamazepine (26, 34, 53). Attention should be given to drugs, especially phenytoin, that may stimulate microsomal enzymes and lead to more rapid metabolism of exogenous corticosteroid, resulting in rejection.

A supportive and behaviorally oriented nursing approach may be facilitated by participation of a psychiatric nurse clinician. Discharge planning should include careful social service attention to home support, transportation, and rehabilitation.

CONCLUSIONS

Psychiatric focus in the next few years is likely to be on selection for transplantation, prediction of noncompliance, and assessment of posttransplant rehabilitation. These are appropriate questions in the current setting of rising health care costs and a short supply of donor organs. We should be asking how to make what is good for some good for many. Psychiatry should establish preoperative interventions to support prospective transplant patients and should explore societal initiatives for greater donation of cadaveric organs.

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Bipolar Affective Disorder and High Achievement: A Familial Association

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The authors studied 442 probands with nonbipolar major depression, 64 with bipolar II disorder, and 88 with bipolar I disorder. Although the proband groups did not differ in occupational or educational achievement, the first-degree relatives of probands with bipolar disorders had significantly higher mean levels of achievement than did those of probands with nonbipolar disorder. This pattern applied whether or not the relatives themselves had bipolar illness. The authors conclude that the socioeconomic advantage previously associated with affective disorder in general may be limited to the bipolar forms.

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Many researchers have shown links between high socioeconomic status and affective disorder. Relevant data have appeared sporadically throughout this century (1) and have originated in such diverse settings as Bahir (2), Iceland (3), Brighton (4), and New Haven (5).

Individual authors have suggested many and diverse explanations, but a composite of their results clearly limits possibilities. For instance, a researcher who finds that patients with affective disorder have higher socioeconomic status than patients with schizophrenia might conclude that patients with schizophrenia but not patients with affective disorder experience a downward drift in socioeconomic status. Other studies finding higher socioeconomic status among patients with affective disorder than among the general population show that this explanation, although possibly true to an extent, is incomplete.

Alternatively, certain individuals may pursue advancement as a substitute for or in sacrifice of familial and subcultural ties. The attendant stresses and lack of support might then predispose to depression. Moreover, certain personality characteristics—high self-expectations, a focus on achievement at the expense of leisure or enjoyment, or low self-esteem met by compensatory efforts toward advancement—may promote both success and depression at the same time.

Attention to diagnostic specificity narrows these alternatives. The stresses described might be expected to promote depression in general but not the more severe or "manic-depressive" forms in particular. Yet, reviews of the subject (1) show that the link between achievement and affective disorder is strongest for these forms. Unfortunately, most of the relevant studies were carried out before the separation of bipolar and nonbipolar depression became conventional. The NIMH Collaborative Program on the Psychobiology of Depression—Clinical Studies paid particular attention to this and other distinctions within the affective disorders. The resulting data are based on large samples of probands and first-degree relatives and are thus well suited to address these issues.

METHOD

Previous reports (6) have described the family study design in detail. Probands with major depression, schizoaffective depression, mania, or schizoaffective

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TABLE 1. Educational and Occupational Levels of 442 Probands With Nonbipolar Major Depression, 64 With Bipolar II Disorder, and 88 With Bipolar I Disorder

Item	Nonbipolar		Bipolar II		Bipolar I	
	Men (N=165)	Women (N=277)	Men (N=21)	Women (N=43)	Men (N=33)	Women (N=55)
Age (years)						
Mean	31.6	38.2	38.6	36.5	36.5	38.5
SD	13.9	14.2	12.8	13.4	12.7	13.8
Educational level						
Rating[a]						
Mean	3.1	3.5	3.1	3.0	3.2	3.3
SD	1.4	1.3	1.4	1.2	1.3	1.3
College graduates						
Number reporting	163	277	21	43	33	55
Number	53	59	6	13	10	15
Percent	32.5	21.3	28.6	30.2	30.3	27.3
Occupational level						
Rating[b]						
Mean[c]	3.8	3.8	3.0	3.5	4.0	3.6
SD	1.7	1.5	1.2	1.2	1.5	1.2
Managers or professionals						
Number reporting	150	242	20	40	31	48
Number	34	58	8	9	4	8
Percent	22.7	24.0	40.0	22.5	12.9	16.7

[a] 1=college graduate to professional training, 7=less than 7 years of school.

[b] 1=higher executive, proprietor of large concern, major professional; 7=unskilled employee, farmer.

[c] Significant difference across all three groups of men (F=3.1, df=2, 216, p=0.049); rating significantly better for bipolar II than for bipolar I ($p<0.05$, Tukey's follow-up test).

mania according to Research Diagnostic Criteria (RDC) (7) were recruited as they presented for inpatient or outpatient treatment at any of five tertiary centers—Columbia University in New York, Harvard University in Boston, Rush-Presbyterian in Chicago, Washington University in St. Louis, and the University of Iowa in Iowa City. Carefully trained raters used the full Schedule for Affective Disorders and Schizophrenia (SADS) (8) and all available sources of information to assess these probands and derive RDC diagnoses. Other instruments included the Personal History of the Depressive Disorders, a collection of questions that detail demographic factors characterizing the individual's childhood and present environment. Among these were Hollingshead ratings of educational and occupational attainment determined separately for the proband and for both parents.

Roughly three-fifths of the probands participated in a family study. Raters blind to proband diagnosis administered the SADS and the Personal History of the Depressive Disorders to all first-degree relatives 17 years of age or older regardless of location. Those living within 100 miles of the center (200 miles for Iowa City) were interviewed in person, if possible; the remainder were interviewed by telephone. Since the Personal History of the Depressive Disorders also includes educational and occupational ratings for both parents of the interviewee, we were able to extend group comparisons to the grandparents of probands. Thus, ratings for grandparents were obtained from direct interviews with the parents of probands. In all cases, subjects did not themselves rate occupational or educational status but instead simply described the individual's last grade completed and the "highest level job" the subject ever had.

For the present analyses, those probands who entered the study with a major depression were divided by whether they reported a history of mania (bipolar I), of hypomania only (bipolar II), or of neither (nonbipolar). The bipolar I group also included those who entered the study while they were in a manic episode. Alternatively, probands were divided by whether the index episode of major depression was marked by the presence of definite delusions or hallucinations (psychotic depression) or not (nonpsychotic depression); patients with a history of only probable mania or only probable hypomania were included in these categories.

Education was rated on a 7-point scale from 1 (graduate to professional training) to 7 (less than 7 years of school). For categorical comparisons across groups we arbitrarily chose college graduate (a rating of 2) as a threshold. Occupation was rated on a 9-point scale from 1 (higher executive, proprietor of large concern, major professional) to 8 (expected wage earner who never worked) and 9 (other—never employed for a 6-month period; includes homemaker, student, physically disabled). For comparisons across group scores we excluded levels 8 and 9 and used 7 (unskilled employee, farmer) as the lowest category. Categorical comparisons lumped together the top two ratings as managerial or professional.

All probands and interviewed relatives rated themselves and their parents according to the Hollingshead scales. Since approximately two-fifths of the probands did not participate in the family study (and therefore did not have interviewed relatives), data for parents

TABLE 2. Educational and Occupational Levels of Relatives of 442 Probands With Nonbipolar Major Depression, 64 With Bipolar II Disorder, and 88 With Bipolar I Disorder

Relatives' Educational and Occupational Level	Relatives of Nonbipolar Probands			Relatives of Bipolar II Probands			Relatives of Bipolar I Probands		
	Total N	N	%	Total N	N	%	Total N	N	%
Fathers									
College graduates[a]	440	71	16.1	64	17	26.6	88	24	27.3
Managers or professionals[b]	436	81	18.6	64	20	31.3	88	25	28.4
Mothers									
College graduates[c]	440	46	10.5	64	13	20.3	88	16	18.2
Managers or professionals[d]	183	23	12.6	32	5	15.6	39	13	33.3
First-degree male relatives									
College graduates[e]	444	106	23.9	70	19	27.1	119	46	38.7
Managers or professionals	419	109	26.0	64	19	29.7	106	40	37.7
First-degree female relatives									
College graduates[f]	584	94	16.1	95	26	27.4	154	49	31.8
Managers or professionals[g]	515	88	17.1	88	23	26.1	132	41	31.1
Grandfathers									
College graduates	250	19	7.6	39	2	5.1	69	9	13.0
Managers or professionals	278	32	11.5	45	4	8.9	75	15	20.0
Grandmothers									
College graduates	256	13	5.1	43	1	2.3	70	5	7.1
Managers or professionals	59	5	8.5	18	3	16.7	19	3	15.8

[a] Significant difference across groups ($\chi^2=8.7$, df=2, $p<0.025$); percent for nonbipolar significantly lower than that for bipolar II ($\chi^2=4.2$, df=1, $p<0.05$) or bipolar I ($\chi^2=6.2$, df=1, $p<0.025$).

[b] Significant difference across groups ($\chi^2=8.32$, df=2, $p<0.025$); percent for nonbipolar significantly lower than that for bipolar II ($\chi^2=5.6$, df=1, $p<0.025$) or bipolar I ($\chi^2=4.4$, df=1, $p<0.05$).

[c] Significant difference across groups ($\chi^2=7.75$, df=2, $p<0.025$); percent for nonbipolar significantly lower than that for bipolar II ($\chi^2=5.3$, df=1, $p<0.025$) or bipolar I ($\chi^2=4.2$, df=1, $p<0.05$).

[d] Significant difference across groups ($\chi^2=10.25$, df=2, $p<0.01$); percent for nonbipolar significantly lower than that for bipolar I ($\chi^2=10.2$, df=1, $p<0.005$).

[e] Significant difference across groups ($\chi^2=10.4$, df=2, $p<0.01$); percent for nonbipolar significantly lower than that for bipolar I ($\chi^2=10.4$, df=1, $p<0.005$).

[f] Significant difference across groups ($\chi^2=21.95$, df=2, $p<0.001$); percent for nonbipolar significantly lower than that for bipolar II ($\chi^2=7.1$, df=1, $p<0.01$) or bipolar I ($\chi^2=19.3$, df=1, $p<0.001$).

[g] Significant difference across groups ($\chi^2=14.32$, df=2, $p<0.001$); percent for nonbipolar significantly lower than that for bipolar II ($\chi^2=4.1$, df=1, $p<0.05$) or bipolar I ($\chi^2=12.85$, df=1, $p<0.001$).

are presented separately. These data represent proband ratings. Data for first-degree relatives in general (including parents) are self-ratings and apply only to those families in the family study. The grandparents of probands were rated by the interviewed parents of probands; therefore, such ratings were also made only for family study probands.

Group comparisons used both continuous and categorical ratings. Analyses of variance (ANOVAs) were used in the former case and chi-square tests in the latter. In both cases, we conducted three-way comparisons and, if the significance level was less than 0.05, we computed follow-up pairwise tests of significance. Analyses were conducted separately for males and females, since cultural determinants for educational and occupational achievement vary substantially by sex.

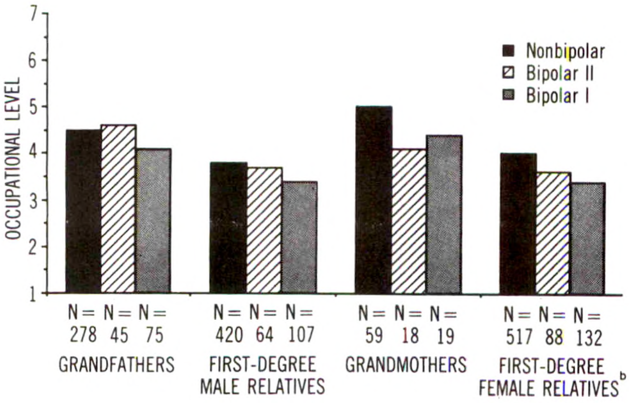
RESULTS

Male probands with bipolar II disorder were particularly likely to occupy managerial or professional jobs, although, as a group, they had not achieved educational levels higher than those for nonbipolar and bipolar I males (see table 1). Female probands did not differ across diagnoses for either educational level or occupational status.

Fathers of bipolar II and bipolar I probands had both higher educational attainment and higher occupational attainment than did the fathers of nonbipolar probands (see table 2). Among the larger group of all interviewed male relatives, those of bipolar I probands had attained higher educational status than had the relatives of nonbipolar probands, but the relatives of bipolar II probands assumed intermediate positions on these measures (see table 2 and figures 1 and 2). Although occupational status did not vary significantly in a three-way comparison, the 106 male relatives of bipolar I probands were more likely to hold managerial or professional positions than were the relatives of nonbipolar probands ($\chi^2=5.70$, df=1, $p<0.025$). Although overall achievement levels were decidedly lower for grandfathers, those related to bipolar I probands were also distinguished by higher educational and occupational attainment (see table 2 and figures 1 and 2).

The mothers of bipolar II and bipolar I probands were twice as likely to be college graduates as were the mothers of nonbipolar probands (see table 2), and the mothers of bipolar I probands were particularly likely

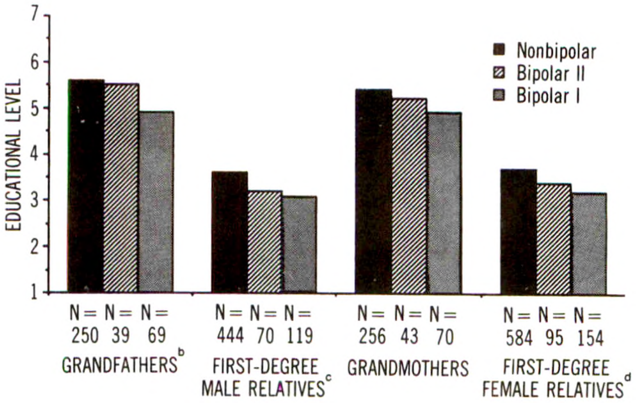
FIGURE 1. Mean Ratings of Occupational Level of Relatives of 442 Probands With Nonbipolar Major Depression, 64 With Bipolar II Disorder, and 88 With Bipolar I Disorder[a]



[a] Higher ratings indicate lower status.

[b] Significant difference across groups (F=11.1, df=2, 732, p=0.0001) and between nonbipolar and bipolar I groups ($p<0.05$, Tukey follow-up test).

FIGURE 2. Mean Ratings of Educational Level of Relatives of 442 Probands With Nonbipolar Major Depression, 64 With Bipolar II Disorder, and 88 With Bipolar I Disorder[a]



[a] Higher ratings indicate less education.

[b] Significant difference across groups (F=4.1, df=2, 355, p=0.017) and between nonbipolar and bipolar I groups ($p<0.05$, Tukey follow-up test).

[c] Significant difference across groups (F=6.41, df=2, 630, p=0.002) and between nonbipolar and bipolar I groups ($p<0.05$, Tukey follow-up test).

[d] Significant difference across groups (F=11.8, df=2, 830, p=0.0001) and between nonbipolar and bipolar I groups ($p<0.05$, Tukey follow-up test).

to occupy professional or managerial positions. Similar patterns held for the larger group of all interviewed female relatives (see table 2 and figures 1 and 2). The grandmothers of bipolar I and bipolar II probands were twice as likely to have had managerial or professional occupations as were those of nonbipolar probands, although differences were not significant.

These variables were also used to compare parents and interviewed first-degree relatives of the 28 psychotic and 197 nonpsychotic male probands as well as the 57 psychotic and 332 nonpsychotic female probands. None of the group comparisons reached statistical significance, nor were there consistent trends favoring the relatives of psychotic probands over those of nonpsychotic probands.

The relatives of bipolar I and bipolar II probands had superior levels of occupational and educational achievement whether or not they themselves had a lifetime history of bipolar illness (see table 3). However, differences across proband diagnostic groups were more striking for relatives who themselves had bipolar illness; these differences resulted from particularly high achievement ratings for relatives of bipolar I probands who themselves had bipolar I or bipolar II illness. Among women related to bipolar I probands, for instance, those with a personal history of mania or hypomania were significantly more likely to be college graduates ($\chi^2=6.8$, df=1, $p<0.01$) and to occupy managerial or professional positions ($\chi^2=9.1$, df=1, $p<0.005$) than were women who, despite their relationship with a bipolar I proband, lacked a personal history of bipolarity.

Thus, bipolar illness in a relative was associated with a socioeconomic advantage only if the relative was related to a proband with bipolar disorder. Bipolar relatives related to bipolar II and bipolar I probands were more likely to have bipolar I illness (two of 18, or 11.1%, and seven of 22, or 31.8%, respectively) than were bipolar relatives related to nonbipolar probands (three of 50, or 6.0%). This did not account for group differences among relatives with bipolar illness, however. When bipolar I relatives were excluded from the analyses displayed in table 3, robust patterns remained favoring bipolar II relatives of bipolar probands over bipolar II relatives of nonbipolar probands. Group comparisons that reached significance in table 3 reached significance in this new analysis as well.

DISCUSSION

These contrasts were restricted to probands with affective disorder and their relatives. Since no general population figures were available, the evidence here suggests only that the family backgrounds of bipolar patients were marked by higher socioeconomic status than the family backgrounds of probands with nonbipolar depression. Only if we accept the rather considerable evidence that severe affective disorder is associated with socioeconomic advantage relative to the general population (1) can we deduce that bipolar illness specifically is associated with better-than-average achievement.

This conclusion is further supported by a smaller study by Woodruff et al. (9), in which bipolar probands and their brothers had higher status ratings than did unipolar probands and their brothers. As in the present study, these differences were more pronounced for educational achievement than for occupational sta-

TABLE 3. Educational and Occupational Levels of Relatives of 442 Probands With Nonbipolar Major Depression, 64 With Bipolar II Disorder, and 88 With Bipolar I Disorder Who Did or Did Not Have Bipolar Disorder Themselves

Relatives' Educational and Occupational Level	Relatives of Nonbipolar Probands Total N	N	%	Relatives of Bipolar II Probands Total N	N	%	Relatives of Bipolar I Probands Total N	N	%
Male relatives without bipolar disorder									
College graduates	431	105	24.4	62	17	27.4	108	38	35.2
Managers or professionals	409	106	25.9	56	17	30.4	96	36	37.5
Male relatives with bipolar disorder									
College graduates[a]	13	1	7.7	8	2	25.0	11	8	72.7
Managers or professionals	10	3	30.0	8	2	25.0	10	4	40.0
Female relatives without bipolar disorder									
College graduates[b]	547	87	15.9	85	21	24.7	143	43	30.1
Managers or professionals[c]	480	80	16.7	79	18	22.8	125	36	28.8
Female relatives with bipolar disorder									
College graduates[d]	37	7	18.9	10	5	50.0	11	6	54.5
Managers or professionals	35	8	22.9	9	5	55.6	7	5	71.4

[a] Significant difference across groups ($p=0.003$, Fisher's exact test, two-tailed); percent for nonbipolar significantly lower than that for bipolar I ($p=0.003$, Fisher's exact test, two-tailed).

[b] Significant difference across groups ($\chi^2=16.2$, $df=2$, $p<0.001$); percent for nonbipolar significantly lower than that for bipolar II ($\chi^2=4.0$, $df=1$, $p<0.05$) or bipolar I ($\chi^2=14.9$, $df=1$, $p<0.001$).

[c] Significant difference across groups ($\chi^2=9.85$, $df=2$, $p<0.01$); percent for nonbipolar significantly lower than that for bipolar I ($\chi^2=9.4$, $df=1$, $p<0.005$).

[d] Significant difference across groups ($p=0.003$, Fisher's exact test, two-tailed); percent for nonbipolar significantly lower than that for bipolar I ($p=0.003$, Fisher's exact test, two-tailed).

tus. Moreover, Woodruff et al. used age-controlled census data to conclude that unipolar subjects were not below population averages in educational achievement.

The data bear directly on several of the previously listed hypotheses. Stress may attend the pursuit of success, and the geographic upheaval and consequent lack of nearby support may well interact with this stress to provoke anxiety, dysphoria, and even major depression. It seems much less likely that such conditions would promote mania or hypomania. Nor does it appear that manic or hypomanic states themselves sufficiently account for these group differences, since relatives of bipolar I or II probands exhibited higher mean status ratings than did relatives of nonbipolar probands, whether or not the relatives themselves had ever had mania or hypomania.

Although membership in pedigrees marked by bipolarity, particularly by bipolar I illness, was associated with socioeconomic advantage, the probands themselves replicated this pattern to only a limited extent. Since a personal history of bipolarity seemed more important among relatives than among probands, severity differences may have operated. Probands were recruited exclusively at tertiary care centers and, therefore, were not only uniformly seeking treatment but had illnesses of sufficient severity and persistence to occasion referral to such centers. The 152 probands with bipolar I or bipolar II disorder had, on average, spent between 3 and 6 months psychiatrically hospitalized over their lifetimes; the 90 relatives with bipolar illness had averaged considerably less than 3 months hospitalized ($t=6.2$, $df=234$, $p=0.0001$). These probands were also significantly more likely than the bipolar relatives to have been incapacitated during a major depressive episode (41, or 27.0%, versus two, or 2.2%; $\chi^2=23.7$, $df=1$, $p=0.0001$). The consequent disability may therefore have overwhelmed any advantage offered by membership in a bipolar pedigree.

More intriguing was the fact that bipolarity in relatives was associated with higher achievement only among relatives related to bipolar probands. It may be that sporadic or nonfamilial bipolar illness differs in important ways from familial forms. Apparently a wide variety of injuries and illnesses can provoke "sporadic" manic syndromes (10), and manic patients with a negative family history show poorer responses to lithium therapy (11–13). Perhaps familial and nonfamilial forms also differ in their associations with socioeconomic advantage.

Recent work (14) has also linked bipolar illness to creative achievements. Affective disorder in that study was generally overrepresented among well-known writers who were permanent or visiting faculty of the University of Iowa Writer's Workshop, but bipolar I disorder was particularly overrepresented. This coexistence of creativity and bipolarity extended to families as well. The present data suggest a more pervasive link to high achievement. Individuals in creative pursuits may be overrepresented in bipolar pedigrees, but these individuals are probably too scarce to produce the differences seen here.

Within this sample, then, bipolarity and high achievement were indirectly linked. Some unknown factor may give rise to either or both bipolar illness and high achievement. The present data go only far enough to localize the association to bipolar illness rather than affective disorder in general. The nature and reasons for this association remain fertile questions for future research.

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Seasonal and Mood Independence of Low Basal Prolactin Secretion in Premenopausal Women With Seasonal Affective Disorder

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To test hypotheses of opposing roles of dopamine and serotonin in prolactin secretion in seasonal affective disorder, the authors determined basal serum prolactin concentrations for premenopausal women, eight with and 14 without seasonal affective disorder, in late afternoon during the follicular phase of the menstrual cycle (and a subgroup during the luteal phase) in winter and summer. Despite their significantly higher Hamilton depression scale scores in winter than in summer, the patients had significantly lower prolactin concentrations than the control subjects in both seasons. These results suggest that low prolactin secretion may be a trait characteristic in seasonal affective disorder.

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Although there has been increasing interest in the antidepressant effects of light in seasonal affective disorder (1–5), the biology of the disorder, with the exception of melatonin secretion (1, 6), has received little attention. Two biological hypotheses, however, have been suggested recently: our group has proposed dopamine involvement in seasonal affective disorder (7–9), and O'Rourke et al. (10) have raised the possibility of serotonin (5-HT) involvement. Research on indexes that reflect the functioning of these monoamines is needed to determine whether these hypotheses should be specifically tested.

Secretion of prolactin is regulated in a complex manner by a variety of neurotransmitters and neuropeptides, but both dopamine and 5-HT play important functional roles. Much evidence indicates that dopamine, most directly via tuberoinfundibular projections to the median eminence, is the primary substance of hypothalamic origin involved in the tonic inhibition of prolactin secretion at the level of the anterior pituitary (11–13); however, research in humans (14) and animals (15) has suggested a strong stimulatory role for 5-HT in prolactin secretion. On the basis of this research, prolactin secretion has been assessed as an indirect indicator of dopamine and 5-HT functioning in several psychiatric disorders (16–18), a strategy that may be fruitful as an initial test of monoamine hypotheses of seasonal affective disorder. We report very low early follicular basal prolactin concentration in seasonal affective disorder that does not vary as a function of season or mood.

METHOD

We studied 22 premenopausal women, eight with seasonal affective disorder and 14 without. All gave informed written consent to participate in the study. The patient and control groups were matched for age (patients: mean±SD=29.6±4.3 years, range=21–34; control subjects: mean±SD=27.9±5.2 years, range=20–34; t=1.18, df=20, p=0.3), weight in the winter (patients: mean±SD=60.8±3.4 kg; control subjects: mean±SD=62.4±4.1; t=1.10, df=20, p=0.3), and weight in the summer (patients: mean±SD=59.0±2.4 kg; control subjects: mean±SD=61.4±3.2 kg; t=1.11, df=20, p=0.3).

All subjects were obtained by media advertisements, and all respondents were then interviewed with a modified version of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (19). This selection procedure is typical in outpatient studies of seasonal affective disorder (1–6). The women with seasonal affective disorder met *DSM-III* criteria for a major depression that developed during the fall, was continuous during the winter, and remitted the following spring for at least the last 3 consecutive years; these patients also met *DSM-III-R* criteria for a seasonal pattern to the major depression. The winter depres-

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sions were not in reaction to seasonally varying psychosocial stressors. The patients also had to be free of depressed periods during the last three consecutive summers. Reports based on the interviews of the patients concerning their behavior during the summer satisfied the hypomania criterion included in the *DSM-III* criteria for cyclothymic disorder; therefore, our patients had the bipolar II form of seasonal affective disorder observed by others (2–4). No other axis I psychiatric disorder existed among our patients. The control subjects were free of psychiatric disorder as determined by the same structured interview. Kappas for independently assigned diagnoses, determined by dual diagnosis from audiotapes of the patients, were 0.88 for major depression, 0.96 for seasonal pattern, and 0.78 for hypomania, values consistent for subjects we have previously studied (20–22). Any subject who reported postmenopausal status, pregnancy, use of birth control pills during the previous 4 months, use of any prescribed medication during the past 6 months, any form of substance abuse, menstrual cycle irregularities, endocrinopathies or other relevant medical conditions, an eating disorder, or epilepsy was excluded from study. None of the subjects had used phototherapy.

Basal serum prolactin was assessed in the winter between Jan. 5 and 21 and in the summer between July 9 and Aug. 21. Prolactin concentration was assessed over a 45-minute period by averaging the value of three blood samples taken 15 minutes apart. The fact that variance among the three prolactin values obtained at each measurement for each subject did not differ significantly as a function of Group (F=3.76, df=1, 20, p=0.1), Season (F=0.05, df=1, 20, p=0.8), or Group by Season (F=0.68, df=1, 20, p=0.4) indicates that the mean of the three prolactin values was equally representative of the prolactin concentration for both groups and both seasons.

The timing of prolactin measurement was controlled: 1) blood samples were collected in the early to mid follicular phase of the menstrual cycle (between days 2 and 7), and the mean±SD number of days into the follicular period for the winter measurement (patients: 6.3±1.5 days, range=2–7; control subjects: 6.0 ±1.2 days, range=2–7) and the summer measurement (patients: 5.5±1.8 days, range=2–7; control subjects: 5.5±1.5 days, range=2–7) did not significantly differ as a function of Group (F=0.06, df=1, 20, p=0.8), Season (F=2.30, df=1, 20, p=0.2), or Group by Season (F=0.09, df=1, 20, p=0.8), and 2) to control for diurnal variation in prolactin secretion and because seasonal affective disorder is associated with a marked worsening of symptoms in the late afternoon (7, 23), blood samples were collected at 5:30, 5:45, and 6:00 p.m.

On blood sampling days, all subjects consumed the same liquid protein drink at noon, fasting before and after except for water. They had abstained from caffeine and alcoholic beverages for no less than 24 hours. We controlled their activity level by having them sit for 40 minutes before blood sampling in a temperature-controlled room with overhead illumination of 300 lux measured at eye level. Blood samples were spun down immediately, and serum samples were assayed in duplicate for prolactin within 1–2 days by using a double-antibody radioimmunoassay. The sensitivity of the assay was 1.0 ng/ml, and the inter- and intra-assay coefficients of variation were 7.1% and 6.3%, respectively.

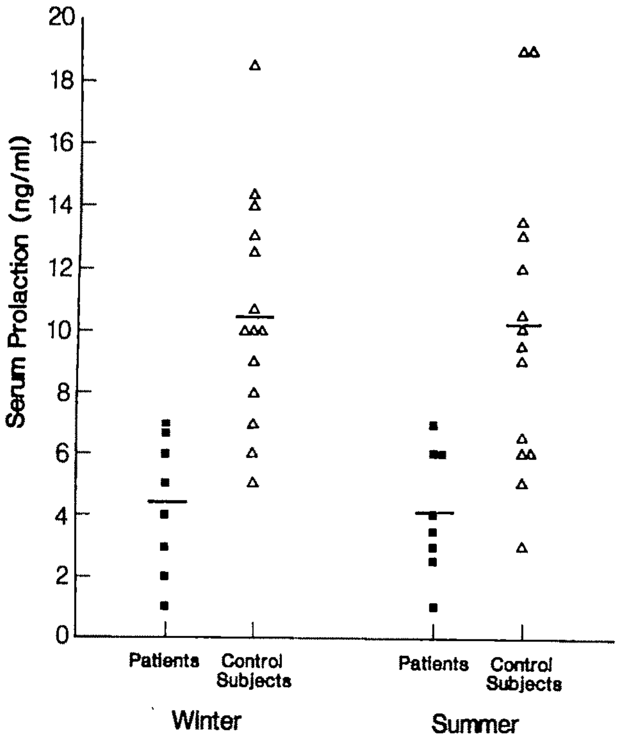
For six of the eight patients and five of the 14 control subjects, prolactin concentrations were also measured 2 weeks later in the winter (between Jan. 19 and Feb. 7) during the mid to late luteal phase of the menstrual cycle (between days 19 and 25). The mean±SD number of days into the menstrual cycle at this assessment did not differ significantly between the groups (patients: 22.6±3.2 days, range=19–24; control subjects: 22.8±1.5 days, range=20–25; t=0.06, df=9, p=0.9).

Depression was blindly assessed in the patients and the control subjects on the day of prolactin assessment by use of the 21-item Hamilton Rating Scale for Depression (24) for which interrater agreement (intraclass correlation coefficient=0.86) was determined by use of audiotapes. To ensure that the depression score derived in winter reflected a relatively stable mood state at the time of prolactin assessment, the Hamilton scale assessment covered the week before and the day of the prolactin assessment. In all cases, level of depression on the day of assessment was equal to or more severe than the 7-day overall level of functioning. To further assess the stability of depression, all patients and control subjects were administered a second Hamilton scale approximately 2 weeks later (the time of luteal prolactin assessment for those participating in this analysis), which also covered a 1-week period. Thus, for all subjects, level of depression was assessed over 2 of the 3 weeks surrounding the prolactin assessment times. In summer, the Hamilton depression scale assessment also covered a 1-week period; periods of depression of any length during the month before prolactin assessment were to be rated on the Hamilton scale, but no ratable periods of depression were reported by any subject for that month. In the summer, the subjects were interviewed concerning hypomanic episodes in the 2 weeks before prolactin assessment, but none satisfied *DSM-III* criteria for hypomania during that time period. Thus, in both winter and summer, mood at the time of prolactin assessment was relatively stable.

RESULTS

The mean±SD Hamilton depression scale scores for the control subjects at the two winter assessments (1.4±1.3 and 1.6±1.4) and at the one summer assessment (0.6±1.1) did not exceed the range of 0–4. The mean±SD Hamilton scale scores for the patients at

FIGURE 1. Basal Follicular Serum Prolactin Concentrations in Winter and Summer of Premenopausal Women With (N=8) and Without (N=14) Seasonal Affective Disorder



these three assessments were 22.8±4.2 (range=17–29), 21.1±3.6 (range=15–27), and 1.8±1.3 (range=0–4), respectively. Because the control subjects had exceedingly low scores at all three assessments and because their scores would be expected to differ significantly from the patients' scores by virtue of their selection for low levels of depression, only the Hamilton scale scores of the patients were analyzed for significant differences across the three assessment occasions. One-way analysis of variance (ANOVA) with repeated measures on the patients' Hamilton scale scores was highly significant (F=328.20, df=2, 14, p<0.0001). The two winter scores did not differ significantly, but both of the winter scores were significantly higher than the summer score (Newman-Keuls tests, p<0.0001). For the subgroup of six patients and five control subjects assessed for luteal prolactin, the mean±SD Hamilton scale scores indicated a similar level of significant depression for the patients at the luteal assessment (patients: 20.8±3.6, range=15–27; control subjects: 1.2±1.4, range=0–4; Newman-Keuls test, p<0.001).

A 2×2 ANOVA with repeated measures revealed no significant differences for basal follicular serum prolactin as a function of Season (F=0.17, df=1, 20, p=0.69) or of Group by Season interaction (F=0.02, df=1, 20, p=0.89), but the patients had lower prolactin values than the control subjects overall; this difference was highly significant (F=18.21, df=1, 20, p<0.0001) (figure 1). Post hoc Newman-Keuls analysis showed that the patients had significantly lower mean±SD prolactin concentrations than the control subjects in both seasons (winter: 4.33±2.21 and 10.57±3.65 ng/ml, respectively; p<0.0001; summer: 4.13±2.05 and 10.14±4.86 ng/ml, respectively; p<0.003). Pearson product-moment correlation between winter Hamilton scores and follicular prolactin values in the patients (r=0.13) was not significant.

A 2×2 ANOVA with repeated measures for luteal prolactin revealed that the prolactin concentrations of the two groups differed significantly (F=16.30, df=1, 9, p<0.001), and post hoc Newman-Keuls tests indicated that the patients had significantly lower prolactin concentrations than the control subjects at both the follicular and luteal phases (p<0.01). The mean±SD luteal prolactin concentrations of the patients and the control subjects were 8.83±3.18 and 13.60±1.64 ng/ml, respectively. Both groups showed the increase in basal prolactin concentration associated with the luteal phase that has been reported elsewhere (25), but the magnitude of this increase did not differ significantly between the groups (Group by Menstrual Phase interaction, F=2.25, df=1, 9, p<0.2).

DISCUSSION

Our results suggest that seasonal affective disorder is characterized by very low late-afternoon, early follicular basal prolactin concentrations. There is no consistent finding of low basal prolactin secretion in women with other psychiatric disorders, including schizophrenia, bipolar affective disorder, nonseasonal major unipolar depression, schizoaffective disorder, mania, and various personality disorders (14, 17, 18, 26–31), although low prolactin concentrations have occasionally been noted in some bipolar patients (32, 33). The difference in prolactin values between our patients and our control subjects cannot be accounted for by nonspecific factors, such as diet, activity level before prolactin assessment, weight, age, menopausal status, medications, time of day of blood sampling, or phase of menstrual cycle. It is also unlikely that personal history of stress or the stress of the experimental procedure contributed to the low values in our patients, since stress stimulates prolactin secretion (34) and none of the patients or control subjects reported fear of venous puncture. Similarly, the effect of daytime naps and perhaps sleepiness, which are characteristics of seasonal affective disorder during the winter, is not likely to be related to the low prolactin results we found, because the effect of these factors is to stimulate prolactin secretion (35) and daytime naps are not characteristic of seasonal affective disorder in the summer, a time when we found equally low values in our euthymic patients.

Our finding of higher prolactin values in our control subjects than in our patients is not unrepresentative: a large published study of basal prolactin secretion, controlling circadian variation, in 75 healthy premenopausal women of similar age and phase of the menstrual cycle as our control subjects (25) found 1) a lowest value of 5 ng/ml (the same as the lowest value for our control subjects in the winter and similar in the summer) and 2) values of 8 ng/ml or higher in 95% of their subjects (compared to 80% of our control subjects).

The low basal prolactin concentration in our patients appears to be a trait characteristic in that it did not vary significantly as a function of season or of marked changes in mood. Two additional findings are relevant. First, because the increase in prolactin concentration during the luteal phase is thought to be due, in part, to an inhibitory influence of some ovarian steroids on dopamine inhibition of prolactin secretion (36–41), the apparently normal increase we found in prolactin concentration during the luteal phase raises the possibility that the generally low prolactin values in seasonal affective disorder are not due to a markedly aberrant ovarian steroid-dopamine interaction. Second, as we reported elsewhere (7), low early follicular prolactin values in five of our patients remained low when reassessed in the early follicular phase after a marked antidepressant response to 2 weeks of phototherapy (2500 lux at 6–8 a.m. and 6–8 p.m. daily). Thus, in five of our eight patients, we found low prolactin concentration on four occasions (in six of the eight, on three occasions): in the early follicular phase during the winter, during the summer, and after successful phototherapy and in the luteal phase during the winter. Although we have not assessed patients with seasonal affective disorder for prolactin concentrations in late spring or early fall, when they are typically euthymic, the summer prolactin concentrations remained low in our patients when they were neither depressed nor hypomanic, and prolactin values remained low in patients with seasonal affective disorder after a marked antidepressant response (7). It seems, therefore, that low prolactin values in seasonal affective disorder are not simply independent of mood polarity but rather are independent of mood alterations in general.

Because prolactin secretion is influenced by numerous peptides and neurotransmitters, specific conclusions are not possible from these findings. If our current results are not specific to the pituitary control system but rather reflect a more generalized, central neurochemical problem in seasonal affective disorder, the findings raise at least two hypotheses worthy of further study. First, as suggested by others (42), low basal prolactin secretion may result from compensatory up-regulation of D_2 receptors in the anterior pituitary due to reduced functional activity of dopamine. A reduction in dopamine reaching the anterior pituitary can result in an up-regulation of D_2 binding sites and an enhanced pituitary responsiveness to dopamine inhibition (43–45), but whether pituitary D_2 receptors are regulated in a manner similar to the D_2 brain receptors thought to mediate behaviors relevant to seasonal affective disorder is uncertain (46–48). Factors that significantly affect the functional influence of dopamine in controlling prolactin secretion and behavior, such as opiates and gonadal hormones (49–55), will require consideration in testing this hypothesis. Second, we have found two additional indicators of altered dopamine activity in seasonal affective disorder that are consistent with the findings from this study. In a preliminary study (9), we assessed spontaneous eye blink rates in seasonal affective disorder because central dopamine activity, via D_2 postsynaptic receptors, modulates the rate of such blinking in primates and man (56–60). Spontaneous blinking in patients with seasonal affective disorder was found to be double the rate in control subjects during the winter as measured by polygraph; however, we have routinely observed in clinical interviews that patients with seasonal affective disorder blink less frequently. Thus, the stress of the polygraphic procedures (e.g., the unfamiliar room and equipment) may have resulted in a release of dopamine on up-regulated D_2 postsynaptic receptors. Dopamine release under stressful conditions is well documented (61). Although our original data on four patients with seasonal affective disorder indicated that their high blink rate decreased with phototherapy (9), the decrease may have resulted from habituation to the testing procedures on the second test after phototherapy, which occurred only 2 weeks after the first test. We have recently studied a large sample of patients with seasonal affective disorder and found that the blink rates of the patients were significantly higher than blink rates of control subjects in the winter and in the summer (unpublished observations). This finding and the prolactin results in the current study are both consistent with a D_2 up-regulation hypothesis. We have also found a deficient heat loss response to thermal challenge, which is a central dopamine-dependent process (62, 63), in seasonal affective disorder during the winter and an overresponsiveness of this system in the summer (8). The dynamic aspects of the heat loss system do not allow simple interpretation in terms of receptor mechanisms, but our data are clear on the winter deficiency of the system and a failure of the system to normalize in summer. Thus, three indicators suggest that dopamine functioning in patients with seasonal affective disorder is not similar to that of control subjects in the winter or in the summer. Increased dopamine functional activity could also account for low prolactin secretion and high blink rates, but such a dopamine condition, if generalized to other central dopamine systems, is not consistent with the observations that dopamine strongly facilitates locomotion and affective behavior (64) and that seasonal affective disorder is characterized by a marked reduction in the facilitation of behavior (7); it is also not consistent with the deficient heat loss response found in seasonal affective disorder during the winter (8).

Low prolactin concentration also raises the possibility of reduced 5-HT stimulation in seasonal affective disorder (31, 65, 66), a possibility supported by the carbohydrate craving of seasonal affective disorder subjects (10). Testing this 5-HT possibility is complicated by the fact that the mechanism underlying 5-HT stimulation in prolactin secretion is not known. 5-HT may stimulate prolactin-releasing hormone, but evidence also exists for interposing dopamine and opiate mechanisms (67). Moreover, inconsistent with this hypothesis is the hypersomnia and poorly facilitated motor and affective behavior of seasonal affective disorder (2, 7, 23), since low 5-HT functioning is associated with hyposomnia and excessively facilitated and labile motor and affective behavior in animals and man (68). Clearly, studies of seasonal affective disorder subjects incorporating specific pharmacologic challenges are required to assess these hypotheses more directly.

The extent to which the current results apply to all seasonal affective disorder subjects is not certain. Our patients are representative of the bipolar II form of seasonal affective disorder described by others (2–5, 23) in that they were obtained, selected, and diagnosed by procedures similar to those used in other seasonal affective disorder studies (1–6). Jacobsen et al. (6), in the only published study of basal prolactin concentration to our knowledge, found slightly but significantly higher basal prolactin concentrations in seasonal affective disorder patients (polarity unspecified) than in control subjects, but interpretation of their findings is confounded: 1) although 80% of both their seasonal affective disorder and control groups were women, phase of the menstrual cycle was apparently not controlled, and since prolactin secretion increases substantially from the follicular to the luteal phase (25) (e.g., the prolactin values in our patients during the luteal phase are similar to the values reported by Jacobsen et al. in their patients), the basal prolactin values for their eight female patients with seasonal affective disorder cannot be meaningfully compared to the values for their eight female control subjects without reference to and control for phase of the menstrual cycle across both groups; 2) similarly, they included pre- and postmenopausal women but did not specify the proportion of each, and since prolactin secretion is altered by menopausal status (12), direct comparison with our premenopausal-only women is not possible; 3) 20% of both their seasonal affective disorder and control groups were men, and since sex differences exist in prolactin secretion (12), comparison with our female-only group is again not possible (Jacobsen et al. noted that female and male seasonal affective disorder subjects did not differ significantly in basal prolactin secretion, but statistical tests comparing eight to two subjects have little power to reject the null hypothesis); and 4) the basal prolactin mean values in the placebo condition for their 10 control subjects are markedly lower than those found in the largest published study of follicular basal prolactin secretion in normal premenopausal women (25) and are markedly lower than the prolactin values for our control subjects. Thus, the prolactin values that we report appear to be the most representative estimate of prolactin concentrations in seasonal affective disorder during both winter and summer seasons.

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Responses to Hypercarbia Induced by Acetazolamide in Panic Disorder Patients

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CO_2 inhalation has been reported to induce panic attacks in panic disorder patients. State anxiety, somatic symptoms of anxiety, physiological changes, and cerebral blood flow (CBF) were monitored in panic disorder patients before and after intravenous injections of 1 g of acetazolamide (13 patients) and saline (10 patients), given under double-blind conditions. In spite of significant hypercarbia, as evidenced by increased CBF in the former group, only one subject reported panic and even that attack did not meet DSM-III-R *criteria. There was only one significant difference between the drug and placebo groups; the acetazolamide group experienced significantly more dizziness.*

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Pharmacological induction of panic is a topic of contemporary research interest. A variety of agents, including sodium lactate, yohimbine, CO_2, and epinephrine, have been found to precipitate panic attacks in predisposed people (1–5).

The relationship between CO_2 and panic is complex. CO_2, which precipitates panic attacks (6–14), has also been found to reduce anxiety (14, 15), and it has been used in the treatment of anxiety (16). Hyperventilation and hypocapnia also cause panic (13, 17). Anxiety induced by CO_2 inhalation decreases with repeated exposures (8) and also after cognitive therapy (12).

CO_2 causes a number of physiological and biochemical changes, both in the brain and in the periphery, several of which have been implicated in the causation of panic attacks (2–5, 7, 10, 11, 13). CO_2 inhalation is accompanied by increased arterial CO_2 levels and reduced pH, which stimulate receptors in the lungs, brain, and carotid bodies (18, 19). These receptors, upon stimulation, cause dyspnea and rapid breathing (19, 20). CO_2 also activates the sympathetic nervous system, causes catecholamine release in the brain and periphery, and increases nonspecific arousal (20–24).

Neurobiological theories of panic, based upon pharmacological induction, rest upon the assumption that these agents act on the brain to precipitate attacks independent of the psychological aspects of the experience. This assumption is only weakly supported, and alternative explanations have been offered (4). Most patients with panic disorder are very anxiety prone, and they frequently suffer from a variety of psychiatric disorders (25–29). It is possible that CO_2 merely induces bodily symptoms of anxiety that trigger panic attacks in patients who have formed learned associations between such symptoms and panic (30, 31). Panic disorder patients also may misperceive these symptoms as a catastrophe such as heart attack or stroke (12, 32).

Increasing CO_2 levels in the brain without exposing the lung and carotid body receptors to high concentrations of the gas might provide clues to the roles played by the central and peripheral factors. Acetazolamide is known to inhibit carbonic anhydrase, an enzyme involved in the transport of CO_2 across membranes (33, 34). Carbonic anhydrase inhibition causes CO_2 buildup in all tissues including the brain. Since CO_2 elimination by the lung is also inhibited, concentration of the gas in the expired air actually decreases (35–38).

METHOD

Twenty-three patients with a diagnosis of panic disorder (*DSM-III-R*) participated in the study. The subjects were free of all medication for a minimum of 4 weeks before the study; this was confirmed with urine drug screens. They were carefully screened for significant physical illnesses with physical examinations, a battery of hematological and biochemical tests, and ECG. None of the patients gave a history indicative of seizure disorders. Written informed consent was obtained from all patients.

Anxiety was measured before and after an intravenous injection of 1 g of acetazolamide (13 patients) or placebo (10 patients), given under double-blind conditions. The patients were assigned to the two groups at random. There were four men and nine women (mean±SD age=37.2±7.4 years) in the acetazolamide group and three men and seven women (mean age =38.1±11.8 years) in the placebo group. The two

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groups did not differ on age (t test) or male-female ratio (chi-square analysis).

The trait scale of the State-Trait Anxiety Inventory (39) and the Beck Depression Inventory (40) were administered at the beginning of the study. During the first and second cerebral blood flow (CBF) measurements, psychic anxiety was measured with the state anxiety scale of the State-Trait Anxiety Inventory (39), and somatic anxiety symptoms were measured with a modified version of the scale developed by Tyrer (30). Tyrer used an analogue scale, while in the present study, symptom severity was indicated on a 0- to 5-point scale. In addition, the subjects were interviewed by the senior author to evaluate the presence or absence of symptoms of panic as described in *DSM-III-R*. Hypercarbia, induced by acetazolamide, can last several hours (38), and, therefore, participants were contacted by telephone the next day and questioned about panic attacks during a period of 24 hours after they left the laboratory.

CBF is very sensitive to CO_2 levels, and hypercarbia is associated with significant CBF increase (41–44). CBF was measured before and after administration of acetazolamide and placebo with the ^{133}xenon inhalation technique (45). A mixture of the isotope in room air (5 mCi/liter) was administered to each patient through a face mask for 1 minute. Isotope clearance from the brain was traced by recording the radioactivity over the scalp for the next 10 minutes with a system of 32 scintillation detectors mounted on a helmet. These clearance curves were analyzed with a bicompartmental model. Gray matter flow was computed from the fast clearing component. Scalp scintillation detector positions were standardized by aligning fixed points on the helmet to the canthomeatal line. Air from around the face mask was monitored for radioactivity, and none of the measurements were associated with leaks. The technique for measuring CBF has been shown to be reliable and valid, and the flow values, thus derived, have been shown to be stable for several hours (46–48). Pulse and respiratory rates, end-tidal CO_2 (Pe_{CO2}) levels, and a one-channel ECG were continuously recorded before and after the injections. Blood pressure was taken manually at the end of each CBF measurement. A venous blood sample was obtained at that time for hematocrit and hemoglobin determinations; the latter was necessary for CBF computations.

The subjects avoided caffeine and nicotine, which are known to influence CBF and anxiety levels (48–52), for a minimum of 3 hours before CBF measurements. CBF measurements were performed in a semidark, quiet room. A butterfly needle with a heparin lock was inserted into a cubital vein and left in situ. The patients relaxed for 15 minutes, and the first CBF measurement was conducted over the next 11 minutes. Two 5-ml blood samples were drawn through the heparin lock; the first one with the heparin from the tubing and needle was discarded, and the second one was used for hematocrit measurements. An intravenous injection of one g of acetazolamide or a placebo was given over 2 minutes. CBF was measured a second time, 5 minutes after the injection. Residual radioactivity from the scalp was recorded for 5 minutes before the second CBF measurement, and the flow values were appropriately corrected. Hematocrit measurements were repeated.

RESULTS

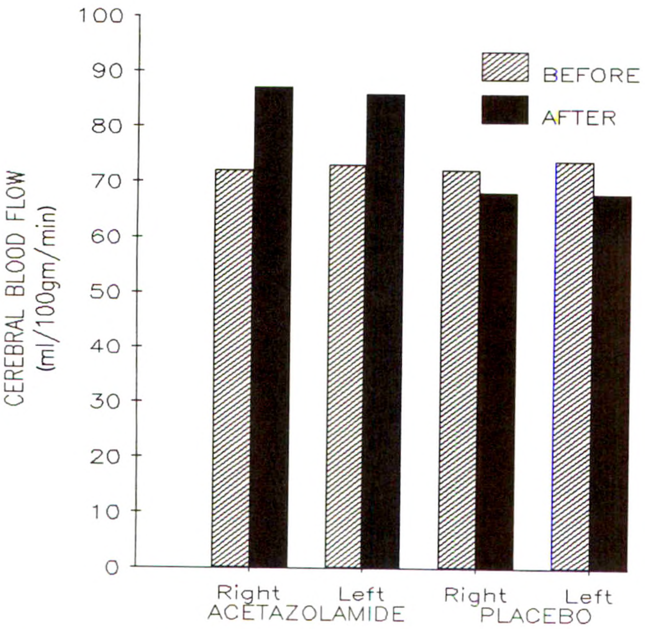
There were no significant differences between the two groups on trait anxiety or depression. The mean ± SD trait anxiety scores for the acetazolamide and placebo groups were 55.9±13.9 and 51.3±9.5, respectively. The mean Beck depression scores for the two groups were 9.7±6.6 and 6.5±3.7.

Only one patient felt that he had a panic attack after injection of acetazolamide. Even that attack did not meet the *DSM-III-R* criteria, and no patients reported attacks after leaving the laboratory. Analysis of variance failed to identify differences in either group on pre-injection and postinjection scores on somatic anxiety symptoms and state anxiety. However, after acetazolamide injection, dizziness increased significantly ($F=6.68$, $df=1, 18$, $p<0.02$). Pre-injection and postinjection state anxiety remained essentially the same for the drug group (mean scores=50.1±16.2 and 52.1 ±12.5), but postinjection state anxiety was significantly lower in the placebo group (mean scores= 45.1±5.5 and 37.3±9.4; $p<0.05$, post hoc Scheffé test).

The two groups were compared on blood pressure (systolic and diastolic), pulse rate, respiratory rate, Pe_{CO2} levels, and hematocrit scores by using a Group by Period repeated measures analysis of variance (ANOVA). The acetazolamide group had a significant reduction in hematocrit after administration of the drug ($F=6.13$, $df=1, 18$, $p<0.03$).

The CBF data were analyzed with a Group by Hemisphere by Period multivariate (repeated measures) ANOVA. A highly significant Group by Period interaction was found. Post hoc comparison (Scheffé test) of the means identified a significant increase in CBF in the acetazolamide group in both left and right hemispheres (figure 1). The control group had no significant change. Similarly, multivariate analysis that examined the regional (frontal, central, temporal, parietal, and occipital) flow values in a single model revealed a Drug by Period interaction that was consistent with the finding from hemispheric means. There were no other interactions. CBF increases after acetazolamide injection and 5% CO_2 inhalation in patients with generalized anxiety disorder and normal volunteers of similar age (from another study [44]) did not reveal significant differences on ANOVA. Pearson correlations between pre-injection and postinjection changes in rating scale scores and physiologic and CBF values did not reach statistical significance.

FIGURE 1. Right and Left Hemisphere Blood Flow in Panic Disorder Patients Before and After Injections of Acetazolamide (N=13) and Placebo (N=10)[a]



[a] There was a highly significant Group by Period interaction (F=21.4, df=1, 18, $p<0.001$).

DISCUSSION

Several investigators have reported panic attacks after the inhalation of 5% CO_2 in up to 70% of panic disorder patients (7, 13). In the present study, only one patient reported panic during hypercarbia induced by acetazolamide injections; even that attack did not meet the *DSM-III-R* criteria. No patients reported feelings of impending doom or desire to flee (13) or panic during the 24 hours after the drug was administered.

CO_2-induced panic has been attributed to several CNS mechanisms (2–5, 7, 10, 11, 13), including acidosis (3, 17). Acetazolamide inhibits carbonic anhydrase, which catalyzes the hydration of CO_2 and hydrolysis of carbonic acid. Inhibition of the enzyme slows down transportation of the gas from tissue to blood and blood to air by approximately 90%, with consequent tissue hypercarbia. Urinary excretion of bicarbonate increases and metabolic acidosis results (33, 34). Since acetazolamide failed to induce panic in panic disorder patients, it would seem that hypercarbia and acidosis are insufficient to precipitate panic. However, such a conclusion cannot be drawn with absolute certainty for several reasons.

The degree of brain hypercarbia induced by acetazolamide is difficult to assess. Once carbonic anhydrase is inhibited, the equilibrium between blood and tissue CO_2 is broken, and blood and end-tidal levels of the gas cease to be reliable indicators of tissue CO_2. CO_2 is well established as a potent cerebral vasodilator (41–44), and acetazolamide is known to increase CBF (39, 53–64).

The CBF increase seen after acetazolamide injection was comparable to that associated with 5% CO_2 inhalation (44), which has been reported to induce panic (7, 9, 10, 13). Although significant global CBF increases were seen after acetazolamide injection, there were no regional differences in the CBF change; CBF change was very similar to the changes induced by CO_2 inhalation (43, 44).

However, the CBF changes induced by acetazolamide and CO_2 may differ in several ways. Although the precise mechanism whereby CO_2 causes CBF increase is unclear, available evidence points to reduction in CSF pH (43). There is little doubt about the hypercarbia and acidosis induced by acetazolamide (33, 34, 37), but it is uncertain whether these are the only mechanisms for the cerebral vasodilation. Other mechanisms are suspected, but none have been demonstrated (38). The drug has no effects on cerebral oxygen metabolism (53, 64). In the present study, subjects who received the drug showed a significant reduction in hematocrit; CBF and hematocrit are inversely correlated (65, 66). We are not aware of any previous reports of this phenomenon, and additional studies are in progress. CO_2 inhalation does not alter hematocrit (44).

CO_2 inhalation increases rate of respiration. Acetazolamide administration was not associated with any significant physiological changes except reduction in hematocrit. Several previous investigators also could not demonstrate an increase in respiration or pulse immediately after administration of acetazolamide (36, 63, 64, 67). The exact reason for this is unclear. CO_2-induced respiratory and circulatory changes are mediated in part through stimulation of the lung and carotid receptors (20). During CO_2 inhalation, concentration of the gas in the lung and blood increases sharply and physiologic responses to CO_2 inhalation (including CBF) are instantaneous (68, 69). Acetazolamide, on the other hand, decreases CO_2 elimination from tissues and it does not increase CO_2 concentration in the lung and blood (35–37). Physiologic responses to acetazolamide, including CBF, are relatively slow to appear and to disappear (38, 53–64).

The first CBF measurement is anxiogenic to most subjects, and the anxiety level usually drops during the second measurement (46, 47, 70). In the present study, this was the case only for the patients who received placebo injections. Patients who received acetazolamide attributed the anxiety to the somatic symptoms. Perception of and response to somatic symptoms are believed by some to be central to the causation of anxiety and panic (4, 12, 31, 32). Panic disorder patients may have learned to associate such symptoms as palpitations and dyspnea with panic, and drugs that induce these somatic symptoms might trigger panic attacks. Acetazolamide did not induce such symptoms as dyspnea or palpitations. However, the acetazolamide group had higher scores on postdrug dizziness, a sense of fullness of the head, and dysphoria. These symptoms might account for the mild elevation in state anxiety in our patients. It should be noted that anxiety is not a known side effect of acetazolamide.

Panic attack has been conceptualized as a phenomenon resembling epileptic seizure (71, 72). It should be noted that acetazolamide is known to possess anticonvulsant activity. It is unclear to what extent the anticonvulsant properties of acetazolamide may account for its inability to induce panic attacks.

Dizziness is frequently associated with CO_2 inhalation, and it has been attributed to hyperventilation and hypocapnia secondary to the associated panic (17). Light-headedness, dizziness, and headaches are commonly associated with cerebral vasodilation induced by a variety of techniques in normal subjects, including acetazolamide injection, CO_2 inhalation, inhalation of volatile nitrites, and administration of volatile solvents and volatile anesthetics (17, 50, 73–75). Thus, in all probability, dizziness was related to the drug-induced hypercarbia and cerebral vasodilation, and not to anxiety.

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Nuclear Magnetic Resonance Study of Obsessive-Compulsive Disorder

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Magnetic resonance imaging (MRI) of the brains of 32 patients who met the DSM-III *criteria for obsessive-compulsive disorder and of 14 normal subjects frequently revealed abnormalities, but none was specific to obsessive-compulsive disorder. Spin-lattice relaxation time (T_1) for right frontal white matter was prolonged in the patients compared to the control subjects, and the patients had greater right-minus-left T_1 differences for frontal white matter. Right-minus-left T_1 differences in the orbital frontal cortex were strongly correlated with symptom severity in the unmedicated patients and in the patients with family histories of obsessive-compulsive disorder.*

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The symptoms of obsessive-compulsive disorder include involuntary and intrusive recurrent thoughts and/or stereotyped behaviors associated with intense anxiety (*DSM-III*). Although drug treatments suggest serotonergic dysfunction in obsessive-compulsive disorder (1), the pathophysiology and neuroanatomy of the disorder remain unknown. Obsessive-compulsive disorder has been observed in the contexts of birth injury, head injury, postencephalitic states, chronic amphetamine intoxication, epilepsy, Parkinson's disease, and L-dopa treatment (1–3). Studies using X-ray CT of patients with obsessive-compulsive disorder have found no diagnostic abnormality (3, 4). Greater ventricle-to-brain ratios have been noted in some patients (5), but not by all investigators (6), and one CT study found smaller volume of the caudate nuclei in patients with obsessive-compulsive disorder (7). Disturbances in frontal and temporal lobe functioning have been described by EEG (1, 2, 4) and neuropsychological testing (2, 4, 5). Studies with positron emission tomography (PET) of patients with obsessive-compulsive disorder have found greater glucose metabolism in the caudate nuclei and left orbital gyrus (6) as well as the right orbital cortex (8). Since effective neurosurgery for intractable obsessive-compulsive disorder interrupts frontal or cingulate fibers (9, 10), these regions may be crucial anatomic substrates in the disorder.

Magnetic resonance imaging (MRI) of hydrogen protons in the brain is more sensitive than CT for detecting abnormalities in many neuropsychiatric disorders (11). Spin-lattice relaxation time (T_1) reflects interactions between excited protons and molecular motion in a chemical environment (12). Resonance signals quantified by relaxation time T_1 may demonstrate abnormalities not visualized by routine imaging of signal intensities (13). Abnormalities quantified by T_1 have been reported in the basal ganglia of schizophrenic patients with tardive dyskinesia (14) and in the frontal-temporal regions of lithium-responsive bipolar depressed patients (15). We found T_1 abnormalities in patients with obsessive-compulsive disorder that suggest involvement of frontal regions.

METHOD

We did MRI studies of 32 patients (20 male and 12 female; mean±SD age=35±9 years, range=20–53) who met the *DSM-III* criteria for obsessive-compulsive disorder and of 14 normal volunteers (nine male and five female; mean±SD age=34±10 years, range=17–55). The patients were recruited from a clinical trial of clomipramine (200 mg/day); 19 were taking the medication and 13 were not. They were taking no other medications and were free of medical, neurologic, and other psychiatric illnesses, including depression (Hamilton Rating Scale for Depression score less than 10), panic disorder, and alcohol and substance abuse. All patients were of at least average intelligence and had had obsessive-compulsive disorder for at least 2 years (mean±SD=17±9 years); the mean±SD age at onset was 18±9 years. Severity of symptoms was rated at the time of MRI by means of the Yale-Brown Obsessive-

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Compulsive Scale (16) (mean±SD severity score=19±8). Family history of obsessive-compulsive disorder was established during patient interview and confirmed by telephone or personal interview of an affected first-degree relative. The volunteer control subjects were not taking any medications and had no history of neurologic or psychiatric illness or substance abuse and no family history of obsessive-compulsive disorder. All control subjects and female patients were right-handed; three male patients were left-handed.

After the subjects gave informed consent, magnetic resonance studies were done at the Harbor-UCLA Diagnostic Imaging Center with a Picker Vista MR system at 1.5 tesla (64 MHz). Images were obtained in sagittal orientation (16 contiguous sections of 5-mm thickness) and axial orientation (12 contiguous sections of 8-mm thickness) with inversion-recovery pulse sequencing (repetition time [TR]=2500 msec, inversion time [TI]=600 msec, time to echo [TE]=40 msec) and in axial orientation (12 contiguous sections of 8-mm thickness) with multiple spin-echo sequencing (TR=2500 msec, TE=40 msec and 80 msec). All sequences used two signals averaged and 192 gradient steps across a 25-cm field of view to reconstruct a 256×256 image matrix.

MRI slice positioning was standardized by reference to internal landmarks on pilot scans of each subject: the apex of the fourth ventricle and the midline corpus callosum on coronal pilot views defined the middle position of sagittal sections; the peaked roof of the fourth ventricle on midline sagittal pilot views defined the base of the slice-select grid for axial sections. Radiologic evaluation was provided by two MRI radiologists (L.C.C. and V.J.G.) who were unaware of the patient or control status of each subject.

The T_1 values were calculated from axial inversion-recovery and spin-echo signal intensities of each voxel and mapped as a set of gray-scaled images (Picker software) exactly congruent with the original sections. Using the MRI video console, a single rater (H.J.G.), blind to diagnosis, recorded the T_1 values for the anatomic areas of interest. In each set of T_1 maps, eight areas were identified in each hemisphere: the head of the caudate nucleus; the dorsolateral frontal cortex at a level two slices above the caudate; the anterior cingulum at a level one slice above the caudate; the central bundle of the frontal white matter and the medial strip of the orbital frontal cortex at the level of the caudate; the lenticular nuclei (globus pallidus–putamen) at the level one slice below the caudate; and the gray and white matter in the medial temporal lobe at a level two slices below the caudate. Although the T_1 maps had excellent tissue contrast, coordinates for anatomic areas were confirmed by reference to the inversion-recovery images of each subject.

Mean T_1 values for each area were computed on-line from the T_1 maps by positioning a circle that enclosed 30 voxels (0.3 cm^2) within each anatomic area. Fourfold magnification of each T_1 map was used for positioning the circle to avoid including edges, focal lesions, and areas with obvious partial-volume effects.

Because different positions of the circle were possible within each anatomic area, we chose the position of greatest homogeneity for T_1; a T_1 value was recorded only if the standard deviation was less than 10% of the mean T_1 value at that position. With this method, repeated calculations of mean T_1 values within subjects varied less than 5% for every anatomic area.

RESULTS

Although radiologic evaluation noted a variety of nonspecific MRI findings for six of the 14 normal control subjects and 14 of the 32 patients, no structural abnormality was unique to obsessive-compulsive disorder. In both patients and control subjects, small foci of hyperintensity on spin-spin relaxation time (T_2)-weighted images were described in a variety of locations in white matter. The anatomic distribution and severity of white matter abnormalities did not differ between groups. Slight prominence or asymmetry of the lateral ventricles was occasionally noted in both groups. No regional asymmetries of signal intensity were observed. None of the MRI findings were considered significant radiologic evidence of neurologic disease.

The T_1 of right frontal white matter was prolonged for patients compared to control subjects (for patients, 490±20 msec; for control subjects, 473±10 msec; Mann-Whitney test, $U=105.5$, $df=44$, $p<0.004$). T_1 values for other brain areas did not differ significantly between groups. T_1 values did not correlate with age for patients or control subjects and did not differ between the sexes in either group.

A test vial (phantom containing 10 ppm of manganese chloride in 1% agar) at a constant position in the MRI head rest revealed that absolute values for T_1 varied up to 15% among subjects. Consistent with previous reports (17), this variability results from small differences in patient mass and position within the imaging field and from fluctuations in gradient and static magnetic fields. Within slices, T_1 values for different positions in a cylindrical phantom varied less than 5%.

Because there was high variability of T_1 values among subjects but good within-slice reproducibility, we used right-minus-left differences in T_1 (T_1 asymmetries) for more reliable comparisons between subjects, as suggested by Breger et al. (17). Bonferroni corrections were made for multiple post hoc comparisons of these differences.

Patients had significantly greater right-minus-left T_1 differences for frontal white matter than control subjects, consistent with prolonged T_1 in right frontal white matter, as we have noted; right-minus-left T_1 differences for other brain areas did not differ between groups (table 1). There was no difference between the

TABLE 1. T_1 Asymmetry (Right Minus Left) for Brain Regions of Interest in 32 Patients With Obsessive-Compulsive Disorder and in 14 Normal Control Subjects Who Underwent MRI

	Difference in T_1 (msec)				Analysis	
	Patients		Control Subjects			
Brain Region	Mean	SD	Mean	SD	Mann-Whitney U (df=44)	p
Caudate nucleus	0	15	−2	11	218.5	<0.62
Lenticular nuclei	12	19	−2	12	123.5	<0.01
Frontal white matter	12	11	1	7	83.5	<0.003[a]
Orbital frontal cortex	5	41	−7	41	186.0	<0.37
Dorsolateral frontal cortex	13	41	−9	37	146.5	<0.09
Anterior cingulum	−9	45	−7	33	221.5	<0.89
Temporal white matter	−3	12	0	17	200.0	<0.44
Temporal gray matter	−8	31	0	18	196.0	<0.35

[a] $p<0.05$ after Bonferroni correction for multiple comparisons.

TABLE 2. Clinical Characteristics of Subgroups of 32 Patients With Obsessive-Compulsive Disorder Who Underwent MRI

	Age (years)		Severity Score[a]		Age at Onset (years)		Duration of Illness (years)	
Patient Subgroup	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Medication[b]								
Taking (N=19)	35	9	18	9	17	8	17	10
Not taking (N=13)	35	9	22	7	19	10	16	8
Family history of obsessive-compulsive disorder								
Positive (N=8)	37	11	16	7	19	9	18	11
Negative (N=24)	34	8	21	8	18	9	16	9

[a] Yale-Brown Obsessive-Compulsive Scale (range of possible scores=0–40).
[b] Clomipramine, 200 mg/day.

sexes in either group for T_1 asymmetry in any brain area.

Because large standard deviations for right-minus-left differences in T_1 suggested heterogeneity, we compared subgroups based on family history and medication status. These subgroups were clinically similar (table 2). Right-minus-left T_1 differences were not significantly different between subgroups based on medication status. Compared to the control group, right-minus-left T_1 differences for frontal white matter were greater for the medicated patients (Mann-Whitney test, U=49.5, df=31, $p<0.002$) and the unmedicated patients (U=34, df=25, $p<0.005$). T_1 asymmetries for other brain areas did not differ between the control subjects and medicated or unmedicated patients.

Patients with family histories of obsessive-compulsive disorder had a more negative mean±SD right-minus-left T_1 difference for the anterior cingulum (−48±33 msec) than the other patients (4±4 msec) (U=34.0, df=30, $p<0.006$) and the control subjects (−7±33 msec) (U=15.5, df=20, $p<0.004$). T_1 asymmetry for other areas did not differ on the basis of family history. Both of the subgroups of patients had greater right-minus-left T_1 differences in frontal white matter than the control subjects (patients with family history, U=11.5, df=20, $p<0.001$; patients without family history, U=72.0, df=36, $p<0.003$).

Symptom severity correlated strongly with right-minus-left differences in T_1 for the orbital frontal cortex in the unmedicated patients and in the patients with family histories of obsessive-compulsive disorder (table 3 and figure 1). In the unmedicated patients there were less significant correlations between severity and T_1 asymmetry directly for the anterior cingulum and inversely for the lenticular nuclei (table 3).

Severity did not correlate with right-minus-left differences in T_1 in the patient group as a whole, in the medicated patients, or in the patients with no family history of obsessive-compulsive disorder. Right-minus-left T_1 differences did not correlate with age for the patients or the control subjects or with duration or age at onset of obsessive-compulsive disorder.

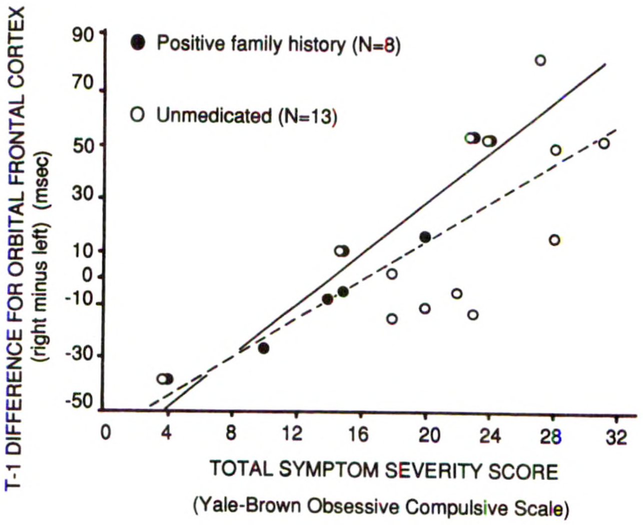
DISCUSSION

Using the nuclear magnetic resonance relaxation parameter T_1 for hydrogen, we observed regional tissue abnormalities in the group of obsessive-compulsive disorder patients when they were compared to the control subjects. Regional T_1 is directly proportional to the averaged mobility of water protons in membranes and fluids (13). Prolonged T_1 is a nonspecific finding, reflecting increased free water or decreased molecular binding of water (13). This could occur in the brain by alteration of extracellular, membrane, or cytoplasmic constituents, by CSF volume averaging, or by blood flow (13). In our study, foci of white matter lesions

TABLE 3. Correlations of Illness Severity With T_1 Asymmetry (Right Minus Left) for 32 Patients With Obsessive-Compulsive Disorder Who Underwent MRI

	Unmedicated Patients (N=13)		Patients With Positive Family History (N=8)		All Patients (N=32)	
Brain Region	r	p	r	p	r	p
Caudate nucleus	0.09	<0.75	0.19	<0.66	0.05	<0.80
Lenticular nuclei	−0.67	<0.01	−0.39	<0.34	−0.31	<0.08
Frontal white matter	0.23	<0.45	0.70	<0.06	−0.09	<0.62
Orbital frontal cortex	0.74	<0.004	0.96	<0.0002	0.10	<0.57
Dorsolateral frontal cortex	−0.11	<0.73	−0.02	<0.96	−0.04	<0.83
Anterior cingulum	0.64	<0.02	0.23	<0.58	0.02	<0.90
Temporal white matter	0.19	<0.54	−0.43	<0.28	0.05	<0.79
Temporal gray matter	0.04	<0.90	0.15	<0.73	−0.06	<0.73

FIGURE 1. Relation of Severity of Obsessive-Compulsive Disorder and T_1 Asymmetry (Right Minus Left) in the Orbital Frontal Cortex of Patients With Positive Family Histories and of Unmedicated Patients[a]



[a] Solid line=patients with positive family histories; broken line=unmedicated patients.

that were apparent on radiologic evaluation were not included in the regional T_1 measurements.

For a variety of technical reasons, T_1 cannot be measured with great precision even in laboratory settings (13, 17). We calculated T_1 values from two signal intensities, which did not exaggerate the variability in absolute values of T_1. Right-minus-left T_1 differences (T_1 asymmetries) within sections were used to improve the reliability of T_1 comparisons between subjects (17). Although the method we used to obtain representative T_1 values from brain areas gave reproducible results, T_1 asymmetry scores had large standard deviations and overlapped between groups. As in T_1 studies of other disorders, this suggests heterogeneity in both normal and obsessive-compulsive disorder subjects and prevents classification based on T_1 values (13).

Right frontal abnormalities in obsessive-compulsive disorder are suggested by our T_1 findings. Prolongation of T_1 in right frontal white matter was supported by our finding of greater right-minus-left T_1 differences for frontal white matter in the patient group as a whole and in the patient subgroups. T_1 asymmetry (right greater than left) in the orbital frontal cortex increased with increasing severity of obsessive-compulsive disorder in the patients not taking medication and in the patients with family histories of obsessive-compulsive disorder. However, left-sided changes may have contributed to right-minus-left T_1 increases, even though lower T_1 was not found in left frontal regions, because absolute values of T_1 varied widely among subjects.

The causes of T_1 abnormalities in obsessive-compulsive disorder are unclear. In the brain, possible origins of altered T_1 include subtle atrophy, which increases CSF volume averaging; redistributions of free water in extracellular and intracellular spaces; and dysmyelination and other conditions that affect the binding of water in molecular structures. Also, T_1 can appear prolonged by decreased blood flow. In normal persons, blood flow is symmetrical in the midfrontal regions and the striatum but greater in the right cingulum than in the left (18). Asymmetry of T_1 (right greater than left) for frontal regions in obsessive-compulsive disorder might relate to abnormal asymmetry of blood flow (right less than left), conceivably in proportion to the severity of obsessive-compulsive disorder. An understanding of T_1 findings in obsessive-compulsive disorder may come from isotope studies of cerebral blood flow or metabolism, biochemical assays by nuclear magnetic resonance spectroscopy, or post-mortem studies.

Right-minus-left T_1 differences in the orbital frontal cortex correlated with severity only in the patients who were not taking clomipramine and in the patients with family histories of obsessive-compulsive disorder; T_1 asymmetry in this region did not differ between all of the patients and the control subjects or between the subgroups based on medication. These observations may reflect the grouping of a heterogeneous population by the diagnosis of obsessive-compulsive disorder, in which there could be a range of disturbances in the frontal white matter and the orbital frontal cortex. Also, relationships of T_1 asymmetry with severity could be obscured by drug effects on regional metabolism or blood flow, which might differ in familial obsessive-compulsive disorder. Studies of obsessive-compulsive disorder patients with homogeneous symptom patterns and measurements before and after treatment with clomipramine may provide clarification.

Hereditary influences on CNS development and expression of obsessive-compulsive disorder have been suggested (1), and these may underlie the T_1 findings in the patients with family histories of obsessive-compulsive disorder (abnormal T_1 asymmetry for the anterior cingulum and strong correlation of orbital T_1 asymmetry with symptom severity, regardless of medication). These findings may be validated by studies of larger samples, although exploration of genetic influences in obsessive-compulsive disorder will require techniques of linkage analysis.

Consistent with CT studies (2–4), MRI did not reveal an association of obsessive-compulsive disorder with overt brain pathology. Focal neuropathology may be relevant for development of obsessive-compulsive disorder in some cases (1–3), but radiologic evaluation of MRI studies on our subjects could not distinguish the patients from the control subjects by MRI appearances. Many subjects in both groups had incidental MRI findings, primarily small white matter lesions, which have been described in normal persons and in patients with a variety of disorders, including dementia (19) and depression (20). Our subjects were free of complicating illness but represented a wide age range. We did not perform morphologic measurements, which might have confirmed CT findings of ventricular enlargement (5) or caudate atrophy (7).

The abnormalities of T_1 that we observed in the patients with obsessive-compulsive disorder suggest involvement of the orbital frontal cortex, frontal white matter, cingulate gyrus, and lenticular nuclei. These areas are components of frontal-limbic pathways that may mediate the symptoms of obsessive-compulsive disorder. T_1 abnormalities in these areas are consistent with frontal dysfunction observed by PET (6, 8) and with improvement after leukotomy (9, 10). Interestingly, pharmacotherapy of obsessive-compulsive disorder appears to affect serotonergic systems, which have projections to the frontal cortex through the striatum and anterior cingulum (21). Our T_1 findings may represent structural or biochemical abnormalities in these regions. Further studies are needed to explore the prevalence and significance of T_1 abnormalities in obsessive-compulsive disorder.

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Sensory Input Deficits and Negative Symptoms in Schizophrenic Patients

David L. Braff, M.D.

The information-processing correlates of positive and negative symptoms in schizophrenic patients are of increasing clinical research interest. The author tested 40 schizophrenic patients and 35 normal control subjects and reports on two major findings. First, patients with negative symptoms had dramatic inflations of stimulus recognition thresholds, similar to the deficits previously reported in patients with head injuries resulting in organic brain syndromes. Second, the schizophrenic patients had deficits in the time-dependent processing of information. Collectively, these data support the link between negative symptoms and multiple levels of information-processing abnormalities in patients with schizophrenic disorders.

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The importance of positive and negative symptoms in the pathophysiology and outcome of schizophrenic disorders has become increasingly clear (1–3). Specifically, it has been proposed that positive symptoms (e.g., hallucinations and delusions) reflect greater dopaminergic tone in "type I" schizophrenic patients (4). Negative symptoms (e.g., anhedonia and withdrawal), on the other hand, are seen as signs of a deficit state or a diminution of important mental functions. The negative symptoms of schizophrenia have been linked to greater ventricular fluid volume, neuropsychological deficits, and, in general, the progressive or deteriorating outcome of "type II" schizophrenia (4). Studies of negative symptoms in schizophrenia have also been associated with a resurgence of interest in Kraepelinian or poor-outcome schizophrenia (5).

In parallel with the focus on positive and negative symptoms in schizophrenia, researchers have examined the attentional and information-processing deficits that accompany schizophrenic disorders. According to this view, the formal thought disorder and cognitive fragmentation of schizophrenic patients are strongly associated with—and may be caused by—an underlying dysfunction of attentional and information-processing mechanisms (6). According to one variation of this position (7, 8), the normal screening of stimuli deteriorates in schizophrenia when attention and information-processing functions are impaired, leading to stimulus overload. This attentional dysfunction causes a secondary cognitive fragmentation, leading to the typical signs and symptoms of psychosis (7, 8). In specifying the neurobiological substrate of this attentional dysfunction, visual backward-masking studies in humans (9) and sensorimotor-gating research in animals (10, 11) have linked time-dependent information-processing deficits to an underlying pathophysiology of greater aminergic tone, both systemically and in specific mesolimbic tracts. Collectively, this research has enabled the attentional impairment and dopamine overactivity hypotheses to be linked together.

In this context, clinical researchers make several assumptions (12). First, they assume that these information-processing functions are important for understanding the cognitive integration of organisms. Second, they assume that these information-processing functions are plastic, or alterable, through changes of their neurobiological substrate. Third, they assume that normal humans operate at a threshold level of attentional operations so that even minor impairments of these critical functions can result in cognitive abnormalities. Fourth, they assume that a primary attentional or cognitive impairment may somehow lead to paranoia or delusional formation.

One major method of measuring attention and information-processing dysfunction in schizophrenia has been the use of a visual backward-masking paradigm (13, 14). In this paradigm, a target letter or symbol is presented either at the subject's recognition threshold or at suprathreshold levels. After a variable interval between stimuli, a noninformational masking stimulus is presented. The masking stimulus erases or interrupts processing of the original target stimulus. As the interval between the target and masking stimuli increases, the target becomes processed before the mask disrupts conscious recognition. Using this paradigm, researchers have shown that schizophrenic patients have inefficient information processing, as reflected by impaired target recognition when the interstimulus interval between mask and target is between 100 and 300 msec

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(13, 14). Schizotypal patients (14), unmedicated schizophrenic patients (15), and even normal subjects with MMPI profiles that reflect schizotypy or vulnerability to schizophrenic psychopathology (16) also have impaired information processing, supporting the interpretation that this impairment at least partially reflects a trait-related dysfunction and is not an effect of neuroleptic medication.

These studies have led to the hypotheses that there are state- and trait-related components to information-processing disruption and that a trait of vulnerability to information-processing dysfunction is accelerated when a schizophrenic patient is in a state of psychotic disruption (13). To study visual backward masking, the visual identification threshold (expressed as milliseconds) for stimuli of standard size and luminance is often determined. Some chronically ill schizophrenic subjects with poor prognoses seem to have impaired identification thresholds for visual information. Saccuzzo and I (17) interpreted our data as supporting the idea that at least some patients with chronic, poor-prognosis schizophrenia may have a two-factor deficit (impaired visual identification thresholds as well as defective stimulus processing in a visual backward-masking task), supporting the original observations of Saccuzzo et al. (18) of selective visual input deficits in some schizophrenic patients.

Although the general deficits in masking performance of schizophrenic patients are clear and replicable (19–21), observations of visual identification threshold deficits in schizophrenic patients have proved to be more confounded. Nuechterlein and Dawson (22) proposed that the critical stimulus duration measure of visual identification may serve as a state marker of psychosis in schizophrenic patients. Alternatively, Merritt and Balogh (23), citing new data unavailable to Nuechterlein and Dawson (22), proposed that the critical stimulus duration task might well be a trait marker of schizophrenia, since asymptomatic students selected according to schizotypic-linked MMPI profiles (higher scores for depression, psychasthenia, and schizophrenia) showed deficits on certain relatively complex critical stimulus duration tasks. Nuechterlein and Dawson (22) emphasized the heterogeneity of various critical stimulus duration procedures, noting that the critical stimulus duration procedure used by Merritt and Balogh was "likely to involve higher processing capacity than the procedure used by Braff and Saccuzzo" (p. 344) and that it was "more likely to detect a deficit among persons at risk for schizophrenia than procedures that involve little or no demand on processing capacity" (p. 344).

In this area of symptom correlates of information processing and backward masking, Green and Walker (20, 21) reported that schizophrenic patients with negative symptoms have poorer masking performance than schizophrenic patients with positive symptoms. These differences seemed independent of experimental attentional manipulation, supporting the idea that a fundamental difference in performance has been found. Green and Walker (20, 21) reported that negative symptoms in schizophrenic subjects with negative or mixed symptoms were associated with impaired information processing. They noted that this result was consistent with previous observations of greater processing deficits in patients with poor prognoses who, theoretically, had greater negative symptom loading. Green and Walker's results are also consistent with Knight's speculation that negative symptoms in schizophrenia are associated with a perceptual organization deficit and concomitant impaired processing (24). The Green and Walker masking paradigm used fixed suprathreshold stimulus durations, so comment cannot be made on issues related to visual identification thresholds.

The study reported in this paper was designed to test several hypotheses linking stimulus identification and information processing to the important emerging theme of symptom correlates of positive and negative symptoms in schizophrenia research. Three hypotheses were tested. 1) Schizophrenic patients with negative symptoms have inflated, impaired visual identification thresholds (critical stimulus durations) compared with patients with positive symptoms. 2) Schizophrenic patients with negative symptoms have impaired information processing on the backward-masking task compared with patients with positive symptoms. 3) On both measures (critical stimulus duration and masking), patients with mixed symptoms would be more impaired than those with positive symptoms through the contribution of a factor associated with negative symptoms. A normal control group was used to assess whether schizophrenic subgroups differed from normal subjects as well as from each other on the dependent measures.

METHOD

The subjects were 40 schizophrenic patients and 35 normal control subjects who were tested in a visual backward-masking paradigm. I was the attending physician for all 40 patients. All patients were hospitalized on an inpatient psychiatry service and met *DSM-III* criteria as well as Research Diagnostic Criteria (RDC) (using the Schedule for Affective Disorders and Schizophrenia [SADS] [25]) for definite schizophrenic disorder (my assessment). Using Andreasen's criteria for positive, negative, and mixed symptom subtypes of schizophrenia (26), an experienced, master's-degree-level research assistant determined the following classifications for the patients: positive symptoms, N=20; negative symptoms, N=6; and mixed symptoms, N=14. I confirmed these determinations.

The normal control subjects had responded to recruitment advertisements and were screened by the research assistant using interviews and questionnaires to rule out major psychiatric disorder, drug abuse, head injury, or major medical problems. All patients and

TABLE 1. Critical Stimulus Duration, Medication, Age, Length of Illness, and BPRS Scores of Schizophrenic Patients With Positive, Negative, or Mixed Symptoms

	Positive Symptoms (N=20)		Negative Symptoms (N=6)		Mixed Symptoms (N=14)	
Variable	Mean	SD	Mean	SD	Mean	SD
Critical stimulus duration (msec)	23.6	35.4	176.2	132.4	74.0	113.2
Medication (mg/day, chlorpromazine equivalents)	1640	1408	1228	1304	1866	1486
Age (years)	25.20	5.04	24.50	3.08	27.36	11.26
Age at onset (years)	18.70	2.72	20.33	2.66	20.25	5.84
Number of years ill	6.50	4.14	4.22	4.61	7.13	6.65
Length of hospital stay (days)	39.8	23.2	40.00	31.1	32.90	18.6
Total BPRS score	45.75	8.85	43.67	1.63	48.93	11.44

control subjects provided informed consent to their participation in the study.

Stimuli were presented in a four-field Gerbrand's tachistoscope. Luminance of the fixation field (0.3 foot-lamberts), the stimulus field (2.9 foot-lamberts), and the mask field (3.7 foot-lamberts) was held constant throughout the experiment. Luminance levels were measured with a Tektronix J16 digital photometer with a J6523 one-degree narrow-angle luminance probe. Measurements for the three fields were taken at the tachistoscope viewing hood in a dark room. Each target letter (either an A or a T) subtended a visual angle of 0.18 degrees and appeared in the center of the visual field of the tachistoscope. The third viewing field was blank to allow adjustment of the interval between the target stimulus and the mask field. The pattern mask, which followed the target letter at varying interstimulus intervals, was constructed by placing black, stick-on, upper-case X's side by side on the fourth viewing field so that the mask was completely superimposed on the target letter.

The critical stimulus duration, a measure of threshold sensitivity, was first obtained for each subject. This measure was defined as the minimal stimulus duration necessary for seven consecutive correct identifications of the target letter without the mask. The target stimulus, consisting of either an A or a T, was presented for 1 msec, and the presentation duration was increased by 1 msec whenever the subject incorrectly identified the letter. Whenever the subject correctly identified the letter, the stimulus duration was left unchanged. At each stimulus duration, regardless of correct response, the target stimulus (T or A) was changed in random order. Backward-masking functions were then assessed. Each stimulus was presented at five fixed masking intervals (60, 120, 300, 500, and 700 msec) between offset of the target letter and onset of the mask or a no-mask condition. After each trial, the subject was informed of the correct letter response.

All patients were additionally rated on the Brief Psychiatric Rating Scale (BPRS) (27) at the time of testing, and a subgroup of cooperative patients received the 64-card version of the Wisconsin Card Sorting Test, a neuropsychological test of cognitive flexibility (28). In the Wisconsin Card Sorting Test, stimulus cards vary along several dimensions (form, number, and color). Subjects use various strategies to sort these cards until they select the experimenter's blindly designated "correct" principle. After a number of correct sortings, the sorting principle is changed and the subject must discern the new "correct" sorting principle through trial and error. The Wisconsin Card Sorting Test yields a score for perseverative responses, reflecting the subject's ability to shift principles according to the experimental demands. In this context, more perseverative errors (reflected by a higher number) indicate poorer performance.

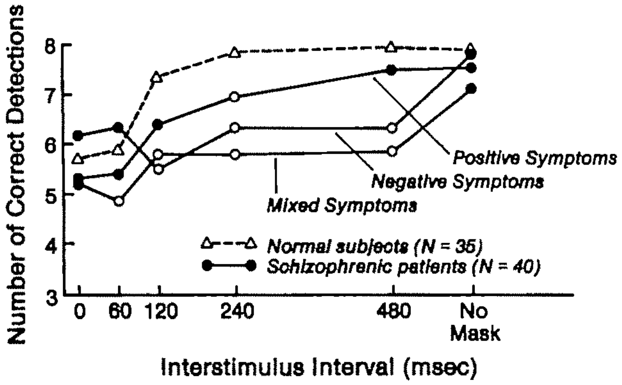
RESULTS

All data were examined in raw form and by analysis of variance (ANOVA) and appropriate post hoc tests. The critical stimulus duration of visual threshold identification for normal subjects was 22.3±66.3 msec, for patients with positive symptoms it was 23.6±35.4 msec, for patients with mixed symptoms it was 74.0±113.2 msec, and for patients with negative symptoms it was 176.2±132.4 msec (table 1). The dramatic differences across the four groups were analyzed by ANOVA, and a significant difference was noted ($F=7.87$, $df=3, 71$, $p<0.001$). Newman-Keuls post hoc analyses (29) indicated that the patients with negative and mixed symptoms were not different from each other but that both had higher values than the patients with positive symptoms and the normal control subjects (all p values were less than 0.01).

To further test the experimental hypotheses, the 20 patients with substantial levels of negative symptoms (the six patients with negative symptoms and the 14 patients with mixed symptoms) were combined and compared with the 20 patients with positive symptoms. The combined group of patients with negative symptoms achieved a raw critical stimulus duration value (104.7±125.2 msec) that appeared to be different from that of the patients with positive symptoms (23.6±35.4 msec); this difference was confirmed by ANOVA ($F=7.76$, $df=1, 39$, $p<0.01$).

Comparisons of the masking data also revealed an interesting pattern of results, reflected by figure 1. Spe-

FIGURE 1. Critical Stimulus Durations and Backward-Masking Results of Normal Control Subjects and Schizophrenic Patients With Positive, Negative, or Mixed Symptoms[a]



[a] Significant differences in backward-masking results for the three groups of schizophrenic patients and normal subjects are indicated by an open circle.

cifically, the performance of all three groups of schizophrenic patients (those with negative, positive, or mixed symptoms) was inferior to that of the normal control subjects at one interstimulus interval or more. The patients with negative or mixed symptoms had more extensive subnormal performance than the patients with positive symptoms. The latter group showed impairment at only the 240-msec interstimulus interval, but the patients with negative symptoms showed impairment at the 120-, 240-, and 480-msec interstimulus intervals and the patients with mixed symptoms showed impairment at the 60-, 120-, 240-, and 480-msec interstimulus intervals. Thus, the patients with negative or mixed symptoms had more profound and extensive masking performance deficits than did the patients with positive symptoms compared with the normal control subjects. On direct intergroup comparison, there were no significant differences between the three schizophrenic groups.

On the Wisconsin Card Sorting Test given to a subgroup of 14 cooperative patients, a more restricted analysis was performed comparing eight patients with positive symptoms with six patients with either negative or mixed symptoms. The results showed a much higher mean±SD number of perseverative errors (5.50 ±2.33) in the patients with negative or mixed symptoms than in the patients with positive symptoms (2.75±2.66). This difference was not strictly confirmed by ANOVA ($F=4.04$, $df=1, 13$, $p<0.067$), possibly due to the small number of subjects.

Demographic and other variables are presented in table 1. There were no significant intergroup differences by ANOVA for age across the four groups. There were also no significant differences across groups in total BPRS, medication (in chlorpromazine equivalents), number of years ill, age at onset, or number of hospitalizations (all p values were greater than 0.05). (The last three variables were measures of chronicity.)

DISCUSSION

This study found that schizophrenic patients with negative or mixed symptoms had dramatically inflated and impaired visual identification thresholds (critical stimulus durations) compared with schizophrenic patients with positive symptoms and normal subjects, despite the matching of the schizophrenic groups for age and chronicity. This result confirms and extends Saccuzzo and my observation that certain schizophrenic patients have a critical stimulus duration deficit that theoretically confounds and exacerbates their information-processing dysfunction (17). The critical stimulus duration data also confirm and extend Green and Walker's hypotheses about the correlation between negative symptoms and information processing in schizophrenic patients (20, 21). It is notable that, of all patients tested in related studies thus far, organically impaired patients who have head injuries have dramatic critical stimulus duration inflations parallel to those of schizophrenic patients with negative or mixed symptoms (30). This pattern of results tends to reinforce the link between the presence of negative symptoms in schizophrenic patients and functional organic brain impairment.

Supporting Green and Walker's hypotheses (20, 21), this study found that the masking performance of schizophrenic patients with negative or mixed symptoms was poorer compared with that of normal subjects than was the performance of the schizophrenic patients with positive symptoms. Still, there were no differences between subgroups on direct comparison. This differential pattern of results may be resolved when the two experimental methods are compared. Green and Walker used a critical interstimulus interval paradigm in which all subjects received a specific suprathreshold stimulus and the interstimulus interval was increased until the target letter was unmasked. The paradigm in this experiment used target letters that were presented at each subject's critical stimulus duration. Since patients with negative symptoms had such dramatically higher critical stimulus durations, they actually had an average of about 150 msec more time to process stimuli than did patients with positive symptoms. Under these conditions, superior performance would be expected because the critical stimulus duration was so much larger for the group with negative symptoms than for the group with positive symptoms. In fact, the schizophrenic patients with negative or mixed symptoms performed slightly worse than those with positive symptoms on the masking task. Under these conditions, the absence of an advantage for the patients with negative symptoms on direct comparison should be viewed as being modestly but indirectly supportive of Green and Walker's hypothesis of impaired information processing in schizophrenic patients with negative symptoms. The comparisons with normal control subjects more directly confirm the association of negative symptoms with increasingly impaired performance on the masking task.

A number of caveats and interpretive points should be noted. First, positive and negative symptoms are probably continuous rather than categorical variables and negative symptoms are not found exclusively in schizophrenic patients. The scale used dichotomized schizophrenic patients into three categories (those with positive, negative, or mixed symptoms). Further, the reader should remember that all three groups were hospitalized for an acute exacerbation of their schizophrenic disorders. Future studies, however, will use Andreasen's more recent quantitative, continuous ratings of positive and negative symptoms (1) rather than the 1982 criteria (26).

Second, the masking functions of patients are not fixed but depend on paradigmatic manipulations of complex variables, including input levels, luminance, and stimulus size (31). In this context, as I have already stated, these data are not directly comparable with those of Green and Walker (20, 21) and are most parsimoniously interpreted as being indirectly supportive of their hypothesis of a differential abnormality of processing linked to negative symptoms.

Third, the group sizes in this study were relatively small, and larger numbers of subjects would be useful in future work to minimize the risk of type II error (missing a difference that, in fact, exists).

Fourth, extensive use of CT scans and neuropsychological test batteries would be desirable in at least some information-processing studies to clarify the correlates of information-processing abnormalities in schizophrenic patients. These studies are currently in progress. Still, on a restricted basis, the results reported here support the idea that negative symptoms in patients with negative and mixed symptoms are associated with impairment in performing the Wisconsin Card Sorting Test. In the small subgroup of patients who took this test, the patients with negative symptoms had twice as many perseverative errors as the patients with positive symptoms, but this was not statistically significant, possibly because of the group's small size. Since performance on the Wisconsin Card Sorting Test is impaired in patients with frontal lobe disorder and in at least some schizophrenic patients (28), this initial result is syntonic with the major finding that negative symptoms may well be associated with cerebral impairment in some schizophrenic patients. To clarify these issues, future research in this area will use larger group sizes and the full Wisconsin Card Sorting Test.

Fifth, control subjects who were patients were not used in this study. Such control subjects would be useful in the future. The use of normal control subjects and the critical subgroup analyses provide important information, however. In future work, various control groups will be studied (e.g., patients with affective disorder and patients with specific brain injuries).

Sixth, interpretations of visual identification thresholds (22, 23) and masking data (30) are extremely complex. Still, mechanisms of masking effects, although far from simple, are interpretable. In the context of this experiment, differential task performance reflected inefficient or impaired processing. Exact underlying mechanisms, even in normal control subjects, remain a controversial topic (31).

The pattern of results leads to a tentative model of the multiple information-processing deficits seen in schizophrenic patients. Even at the relatively automatic level of stimulus identification (critical stimulus duration), there are abnormalities. Saccuzzo and I (17) originally hypothesized that some schizophrenic patients with poor premorbid status and poor outcome had deficits at this fundamental stage of information intake, and subsequent data have supported this position. Whether such a defect is state or trait linked is a complex question, but this study presents direct evidence that negative symptoms are strongly associated with an observed critical stimulus duration deficit. Since organically impaired patients with head injuries are another major group exhibiting such inflated critical stimulus durations (30), these data point to bridges between information-processing intake deficits, negative symptoms, and organic brain impairment. Additionally, although positive and negative symptoms are associated with information-processing dysfunction, it seems as if negative symptoms are associated with more extensive and multiple levels of information-processing abnormalities, supporting and extending Green and Walker's important observations (20, 21). From a theoretical viewpoint, time-linked abnormalities in information processing that occur in an epoch of several hundred milliseconds after stimulus intake fit the temporal "footprint" of monoaminergic neurons (12). Methylphenidate induces a pattern of deficits similar to those observed in the patients with positive symptoms, which supports the association of monoaminergic overactivity with such time-dependent information-processing deficits (9). The more ubiquitous deficits of the patients with negative symptoms may be due to an added general factor associated with global brain impairment, and this may explain the generalized poorer performance of the patients with negative symptoms compared with the performance of the patients with positive symptoms. Future work is needed to sort out these issues.

The two-factor model of information-processing deficits in schizophrenia can now be extended to hypothesize that negative symptoms in schizophrenic patients are associated with a double burden of abnormally inflated stimulus identification thresholds (critical stimulus durations) and inefficient, fragmented information processing (poor masking performance). The current data also indirectly strengthen the theoretical links between negative symptoms and organic brain impairment in general and specifically in schizophrenic patients. It is also possible that inflated critical stimulus durations will serve as a marker for negative symptoms and organic brain impairment in schizophrenic as well as other patients. This study also illustrates the utility of using selected psychophysical tasks that sensitively tap various aspects of brain function. Information-processing tasks deserve more scrutiny in a prospective study using information-processing measures, CT or magnetic resonance imaging (MRI) scans, and extensive neuropsychological tests in combination with ratings of positive and negative symptoms in schizophrenic patients.

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Audiotape Playback as a Technique in the Treatment of Schizophrenic Patients

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The authors report on the use of playing back audiotaped portions of the speech of two schizophrenic patients during psychotherapy. They believe that this audiotape replay was instrumental in organizing the patients' thoughts and spoken communications and that it might also have facilitated the patients' participation in psychotherapy. The usefulness of this strategy is illustrated with clinical material.

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Formal thought disturbance and language abnormalities often constitute striking features of schizophrenia (1). Language disturbances can persist, although diminished, as florid symptoms remit (2–4). Disorders of language are prominent in the subgroup of schizophrenic patients characterized by chronic deterioration, social and occupational debilitation, and a preponderance of negative symptoms (5).

Communication disorders in schizophrenic patients may be due to biologically based deficits in language-processing capabilities, may be the effect of psychological conflicts on learning, or, even more likely, may be some combination of innate and learned dispositions. Whatever the etiology, an intervention that addresses these communication problems may prove valuable in alleviating the disabilities in social and occupational functioning that stem from impaired communication and may enhance the ability of the patient to participate in psychotherapy.

The purpose of this paper is to describe a technique of audiotape playback that seemed to facilitate verbal communication between a therapist and each of two schizophrenic patients. The facilitation may have occurred through the patients' increased ability to attend explicitly to their language and/or thought defects and through an increased objectification of themselves, particularly in relation to the therapist.

The audiotape recorder has been used in psychotherapy research involving detailed content and process analyses and in the training of therapists (6–8). In psychotherapy and psychoanalysis, audiotaping and audiotape playback have been used to help resolve therapeutic impasses, accelerate the progress of an ongoing treatment, intensify the transference, and thwart repression between sessions (9, 10). Among the many therapeutic benefits attributed to audiotape playback are patients' increased awareness of defenses, elucidation of transference distortions, and stimulation of memories and free associations (9–13). Reports of such benefits have centered around expressive therapy with less severely disturbed patients. To our knowledge, the use of audiotape playback in individual dynamic psychotherapy with highly disturbed patients has not been previously described.

USE OF AUDIOTAPE PLAYBACK

The aim of the intervention described here was to help correct language abnormalities by bringing them to the awareness of the speaker (the patient). Just as the therapist's use of confrontation serves to bring into consciousness that which is unacknowledged, the identification of language abnormalities on the audiotape was intended to enhance awareness of such phenomena. Both patients described in this report had considerable conceptual disorganization; they displayed various forms of language disorder (e.g., derailments, incoherence, loss of goal, and word approximations) as well as defects in their sense of personal agency and perception. Neither patient manifested overt psychotic symptoms such as hallucinations, ideas of reference, or delusions during the times covered in this report. However, both patients had experienced psychotic symptoms in the past and both patients met *DSM-III-R* criteria for the diagnosis of schizophrenia.

Each patient was treated in weekly 45-minute psychotherapy sessions for 14 months with the same therapist before the audiotape recorder was introduced. The recorder was positioned on a table situated between the patient and the therapist, who were seated facing each other. Initially, the first 20 minutes of a

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session were recorded and then played back; the audiotape was stopped when the patient or therapist desired clarification of material that had been played back. After a short time of experience with the procedure, the patients initiated more of the requests for clarification and replay of material. They were pleased to have manual control of the machine and were at ease with the apparatus from the beginning.

CASE MATERIAL

Case 1. Ms. A, 55 years old, lived alone and was unemployed. Her first serious paranoid episode required hospitalization at the age of 25. Although she led a reclusive, isolated life, she had worked until 8 years before the time of this report. Since leaving her job she had had virtually no contact with people. Her weekly treatment began 14 months before the time of this study, after her second hospitalization.

Ms. A's presenting complaint was, "I have to be able to think more clearly about what happened to me so that I can go to a lawyer and sue my parents for abuse." She believed that her mother had hypnotized her as a child and gave her medication that would cause her to be confused about her past.

She said that she could "never speak, never find words." She claimed that she often felt invisible, lacked a concept for herself, and had never been believed by her parents, teachers, or doctors. In the beginning phase of treatment, she offered little spontaneous material. Her descriptions of some events (e.g., cooking, shopping, managing her finances) were quite lucid. However, many of her descriptions and recollections were extremely difficult to understand. In these instances, her speech would accelerate, she might confound subject and object, and her use of verbs would become confusing. She would produce vague, convoluted constructions, such as, "I'd never find the words and if I found the words I wouldn't know if they were the same ones I'd used yesterday and if I used different words then I wouldn't know what it meant."

The primary activity in therapy became the reading and discussion of a weekly essay that Ms. A brought to the sessions. Early on she decided that she would write what she wanted to report to the therapist, since she complained of going blank when questions were posed during sessions. In her essays Ms. A focused on internal states as she struggled to differentiate affective from bodily states. In sessions, she occasionally experienced blurring with the therapist.

Ms. A was distressed by her perception of a discrepancy between what she said and what she meant. As her trust in the therapist grew, the therapist suggested that the audiotape playback might help her test her perception of this disparity. By the time the audiotape recorder was introduced, Ms. A's dose of perphenazine had been tapered from 40 mg/day to 2 mg/day. Over the 14-month period before audiotaping began, her suspiciousness in sessions, which occasionally had escalated to hostility, had largely subsided.

Before the audiotape playback intervention, a typical exchange between Ms. A (A) and her therapist (T) was as follows:

> T: How would you describe yourself?
>
> A: Oh, I can't. I could never do that, I wouldn't know how. I never had a concept for myself.
>
> T: What do you look like?
>
> A: I'm fat, I guess.
>
> T: Anything else?
>
> A: I wouldn't know what to say. Why do you keep asking me about myself when I told you I don't know anything about myself. How am I supposed to know?
>
> T: When did you last look at yourself in a mirror?
>
> A: I don't have any mirrors in the house. Wait, I guess there's a small one above the bathroom sink but I covered up all the other ones.
>
> T: When? Why?
>
> A: Years ago, I really don't like looking at myself, I'd never know what to make of it.

The therapeutic effects derived from the audiotape playback intervention were twofold: an enhanced reality perception through objectification of her own mental processes and an explicit consideration of herself within the context of her relationship to the therapist.

When she listened to the audiotaped material, Ms. A was concerned with the properties of her voice—its pitch, clarity, resemblance to other natural sounds. She did not address the content of her narratives. She wanted to use the audiotape recording to hear her own voice, literally. She was a virtual stranger to everyday objectifying experiences (e.g., looking at herself in a mirror or in photographs, appreciating herself as others might perceive her through relationships). At her home she listened to the audiotapes several times a day for the first 2 weeks but then decreased the frequency to one to three times a week between sessions.

When she listened to the playback, she was puzzled yet enthusiastic. After listening to the playback, Ms. A wrote,

> I still can't seem to get a handle on my voice. At times I am just surprised and it sort of turns my mind over until I can somehow accept the fact. But sometimes I make more sense than I think I do, I even sound confident. At times it sounds almost sugary. Trying to recall how I felt when I said it is difficult, but I know I don't ever feel that way. It certainly makes me wonder what people think of me but then appearance counts just as much. Even if I was able to watch myself in the mirror I would have difficulty. I really wonder how much of my real self is apparent to others. I just don't know what you or anyone could know about me—am I really that much of a big coverup or are things apparent?

In Ms. A's case, the psychological value of audiotape playback seemed to parallel the value of the weekly essays. Both devices provided reality-testing functions such as boundary delineation, secondary process thinking, and objectification of the self. Writing, rereading, and again listening contributed to the objectification process.

Before the audiotape playback intervention, Ms. A considered the therapist impervious to what she might do or say. A representative excerpt from one of her essays illustrates her expectations:

> You said I should go to a doctor for my chest pain. I really don't understand how you could be concerned about me. I'm like a capsule, walled off, insensate and invisible. You listen but I don't know why—I feel like I'm not even here.

In the early weeks following the introduction of the audiotaping, the most striking development was Ms. A's emergent sense of herself as a person perceived by others. Later, she developed the idea of herself as one who might affect others—the therapist in particular. From these conceptions flowed two discrete behavioral events: Ms. A began to eat in public settings, and she went to a store to buy new clothes (she had not done this in 8 years). Ms. A acknowledged these features as new things for her and suspected that their appearance had something to do with thinking about how other people must see her.

There was an association in time between these specific therapeutic gains and the initiation of audiotape playback. Ms. A had been in treatment for 14 months before the introduction of this intervention. During that time she had not improved in areas that bothered her. She was baffled by how her mind worked and became irritable when the therapist attempted to explore this with her. Also, she was often unable to maintain distinctions between herself and her therapist.

Ms. A herself identified the playback procedure as being instrumental in the changes noted here. Her experience of listening to her audiotaped voice was both similar to and different from another patient, Mr. B, described next.

Case 2. Mr. B was a 28-year-old schizophrenic man who lived with his disturbed mother and a sister. He became manifestly ill at age 16 with symptoms of excitement and auditory hallucinations; he was hospitalized for similar symptoms about once a year over the subsequent 12 years. He has had a deteriorating course; at one time he had been able to live a highly social and independent albeit unstable life, attend school, and hold menial jobs for a short time. Over the past several years, however, he had remained at home, spending his days walking on the beach spinning elaborate fantasies. At the time of the study, his hallucinations and bizarre behavior had been controlled for 18 months by neuroleptic medication (fluphenazine, 30 mg/day).

Mr. B expressed a desire for an individual relationship with a therapist in preference to the mother-son family treatment that had been recommended. This request was granted, and he attended individual sessions regularly. He identified his problems as suffocation by his mother, sadness associated with his father's death when Mr. B was a child, confusion about social and sexual relationships, and difficulty in thinking clearly and in conversing.

Mr. B described a growing awareness that he was so preoccupied with conforming to the demands and expectations of his mother that he became confused as to his own opinions and desires. He claimed that his mother had never given him credit for original thoughts, and he doubted whether, in fact, he could generate any. He was uncertain of whether his beliefs about having had former lives and having a shared soul with animals were real or fantastic.

Mr. B used an idiosyncratic set of metaphors (cameras and telescopes) to describe how his mind worked. He spoke of the need for delay before he could respond to a question or take action. He would use his camera to take snapshots from different angles and then examine these psychic photographs in order to choose the perspective he wished to adopt. He used the telescope metaphor when he wanted to examine a situation in a continuous fashion through the lens of normal people.

Audiotaping was begun after 14 months of treatment. At that time Mr. B's social activities were increasing and had led him to a heightened curiosity about (and frustration with) his patterns of verbal expression. He claimed that his speech was produced at a much slower rate relative to the speed of his thoughts; he worried that he was losing information. He had the sense that his internal thoughts were inadequately translated into spoken words, which led to misrepresentation of himself in conversation. He displayed loose associations, inability to assign words to his thoughts, rambling narratives, and occasionally stilted and idiosyncratic language. He observed that his listeners often seemed lost when he talked to them.

The therapeutic effects of audiotape playback for Mr. B can be conceptualized as improvement in disorganized thought, self-objectification, and a more realistic consideration of the treatment relationship.

Before the use of audiotaping, Mr. B seemed uninterested when the therapist pointed out gaps in his narrative, despite his claim that he wanted to understand his communication problems. Mr. B's descriptions of events would take a global form; when questioned about details, he often said that he did not know or that he forgot. In contrast, the material he produced when memories and associations were stimulated by audiotape playback were richer and more easily and explicitly incorporated into the therapeutic work. When segments of the audiotape were replayed, Mr. B was able to hear the gaps (loose associations) in his narrative. Initially, the therapist pointed out these derailments to Mr. B. However, within several sessions he was able to identify them himself and stop the audiotape at such points. When he perceived a gap, he often produced a cascade of highly specific memories or associations. These memories were considerably more detailed than the material he generated in the absence of such audiotape stimulation. For instance, after hearing himself on audiotape say, "So after the party we went driving around and he took me to the diner and I got clams. I'll never be able to trust my sister again, though she is a good cook," Mr. B (B) said,

> B: I guess it does sound weird . . . okay, wait, I know. The day my mother remarried we all went to that diner.
>
> T: When was this?
>
> B: I think I was 12 and my sister was 10. And she was trying to get her kite to fly in the parking lot. I helped her build it and she always asked me for help. But that day she went to him [Mr. B's stepfather] and I never wanted to play with her again and we've never liked each other.
>
> T: But with your mother in the hospital [now], it's just the two of you alone.
>
> B: Yeah, she is a good cook, but it's hard to like her. I don't want her taking care of me.

This example is typical of Mr. B's ability to repair loose associations in the context of audiotape playback.

Soon after the use of audiotaping, Mr. B began to incorporate the audiotape recorder into his repertoire of thought processing representations. In contrast to the metaphorical camera, which enriched the visual representation of events, the audiotape recorder was more conducive to organizing spoken thoughts, since its sensory medium was auditory and its action was one of emission (speaking) rather than display.

Mr. B said that he could make his thoughts go on fast forward or reverse. That is, he could project ahead to consider the consequences of an intended response (telescope analogue) or he could do an instant replay and reexamine a situation and decide on a verbal option (camera analogue). He said that he practiced these exercises and was more at ease with other people as a result. Also, he reported using the metaphorical audiotape recorder to monitor conversations: when he felt he was losing someone while talking with them, he would rewind and explain again. He also reported that his racing thoughts had stopped. He was not sure how this happened, but he suspected that it had something to do with "feeling in more control of myself, like I am with the tape recorder."

In the sessions, Mr. B would use audiotape playback to express previously warded-off impulses. He would regularly replay segments, often going over and over a specific sequence. These segments typically involved negative comments about his mother. He liked to hear himself expound on certain personal theories that his mother had previously censored. He mentioned that he also enjoyed listening to the therapist in the act of taking him seriously. In general, however, the interactive dimension of the replayed sequences were of less interest to him than his own soliloquies. He would effectively try himself out on himself. For the first time, he tentatively began to criticize the therapist. Subsequently, he experienced the therapist as tolerant of his remarks and curious about them. These trial actions seemed to be helpful in establishing a more objective sense of himself.

With audiotape playback, Mr. B became observant of the therapeutic relationship in a manner that represented an ability to anticipate events more realistically. Before audiotaping, he referred to the therapist as his princess and the consulting room as his kingdom. After audiotaping, he became increasingly able to talk about a more realistic concept of his relationship with the therapist. His observation of his own repertoire of responses to others complemented the progress in self-objectification process described earlier. For instance, after hearing himself on audiotape say, "Don was 15 years older than me. He was a waiter. We lived together for 10 months," he went on to describe their cohabitation further:

> I've never been able to trust anybody but my father. Maybe you and I once thought Don too. That's why I can't hold a job, I can't take orders from anyone who is not my father. It wouldn't seem right, so I quit. I used to feel guilty about my relationship with Don because I felt that I was supposed to be having some of those feelings with my father, but what could I do, he was dead. I think my life stopped then, in a way. If I get too close to you, I wonder if I'll feel guilty.

DISCUSSION

We have attempted to demonstrate that the process of listening to their own narratives engendered change in two schizophrenic patients with formal thought disturbances.

Broadly speaking, we think that audiotaping seemed to function as an ego extender by providing the patients with conscious control of a device that mimicked and augmented such mental functions as memory, perception, reality testing, self-other differentiation, delay, and trial action. Whatever the etiology of these defective processes, the patients described here seemed to have benefitted from having the greater control over their cognitive functions made possible by audiotape playback.

Enhancement of these functions was manifested, in part, as observable changes in the patients and in their treatment relationships. The changes can be broadly conceptualized as improvement in thought organization, enhanced ability to objectify the self, and appearance of the patients' explicit consideration of their participation in the treatment relationship.

A specific dimension of improved thought organization was the ability to repair fragmented verbal productions as demonstrated by Mr. B. Through playback, he could address the audiotape content directly for discrepancies of flow and coherence. As the clinical material indicated, he was prompted to produce associative material and rich memories. With the help of audiotaping, Mr. B was able to bridge discontinuities in thought generation and expression and to make his productions more meaningful to the listener and to himself.

Further psychological movement was reflected in the strengthened self-objectifying capacities of both patients. Reexperiencing himself on audiotape helped Mr. B fortify an emerging sense of autonomy and ownership of his ideas and reactions. Ms. A's progress comprised an expanding awareness of herself in relation to others, both as someone perceived by others and as someone capable of having an effect on others.

In another manner, audiotaping functioned as an ego extender in the interpersonal relationship with the therapist. By being able to take the concrete audiotape representation of the interaction with the therapist into a solitary context and to reexperience the relationship without the need for immediate action (a function much like memory, recall, and trial action outside of the session), the patients seemed to have been able to develop a sense of themselves in relation to the therapist more rapidly, with a subsequent increase in self-other differentiation, autonomy, and realistic sense of the therapist. By being able to have the voice of the therapist present and heard under conditions they themselves chose, the patients were able to have a clearer conviction that the therapist existed outside of their immediate presence. Thus, these functions made it easier for the patients to participate in psychotherapy.

There are two lines of clinical evidence to suggest that these gains were causally related to the audiotape playback intervention. First, the changes that were observed occurred in temporal relation to the beginning of the audiotape playback after 14 months of little progress with conventional methods. Second, the changes were ascribed to the audiotape playback by the patients themselves.

It is possible, of course, that the audiotape playback method may have enhanced the patients' mental functioning by the nonspecific mechanism through which the therapist's enthusiasm and interest in the method (particularly in the face of previous frustration) were conveyed. There are no clinical data to support or refute this alternative hypothesis.

There may be relative contraindications to the use of audiotape playback with schizophrenic individuals who are suspicious or paranoid, who have delusions about machines, or who have a history of decompensation in the context of audiotape or videotape recording. Auditory hallucinations, poor concentration, or marked distractibility may compromise the patient's ability to use the playback. A patient's unwillingness or hesitation to participate would likely be an absolute contraindication.

Based on the work described here, audiotaping may be a useful intervention for patients who manifest a sustained language disturbance in the absence of active psychosis and who are motivated to align a perceived discrepancy between inner thoughts and spoken verbal expressions. At this point it is unknown whether the audiotape playback can achieve targeted gains or, rather, if it accelerates the therapeutic change or changes that would have otherwise occurred. It is quite possible that the nature of the effect—whether it is specific or global—will depend on the particular patient. At this time, neither generalizations about the indications for use to a larger number of patients nor predictive statements about the nature of therapeutic gain can be made. Our clinical experience suggests that the use of the technique for promoting language organization, enhanced self-objectivity, and a sense of self within the treatment relationship with schizophrenic individuals be investigated further.

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Psychopathology of Very Mild Dementia of the Alzheimer Type

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The authors describe psychiatric abnormalities, including personality and affective changes and psychotic symptoms, associated with very mild senile dementia of the Alzheimer type. The behavioral and affective changes in the subjects with very mild dementia resembled those occurring in subjects with mild dementia, but psychotic symptoms rarely occurred until the dementia had progressed to at least a mild stage.

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Dementia of the Alzheimer type is a devastating disease resulting in deterioration of memory, abstract thinking, judgment, and functional abilities. Accompanying these cognitive changes are psychiatric abnormalities, including such personality changes as explosiveness, rigidity, and withdrawal (1–6), affective changes (7–9), and such psychotic symptoms as delusions and hallucinations (10–15). Recently, there has been renewed recognition and interest in these noncognitive psychiatric manifestations of Alzheimer's disease (16–20).

Careful characterization of the personality changes, affective changes, and psychotic symptoms of Alzheimer's disease has been limited by difficulties in diagnosing as well as staging the severity of the illness. In order to define the natural history of senile dementia of the Alzheimer type, our group at Washington University's Alzheimer's Disease Research Center has been involved in several longitudinal and cross-sectional studies (21–23). To ensure that symptoms were related to senile dementia of the Alzheimer type, we excluded subjects with potentially confounding medical, neurologic, or psychiatric disorders (including depression, psychosis, and alcoholism) from the study. The Clinical Dementia Rating is a scale that was developed to stage the illness into one of five groups: absent, questionable, mild, moderate, and severe (ratings of 0, 0.5, 1, 2, and 3, respectively) (21, 23, 24). The reliability of this scale (25) and the validity of our diagnostic approach (26) has been demonstrated by neuropathological confirmation of Alzheimer's disease in a consecutive series of 31 autopsies of study subjects.

The longitudinal and cross-sectional evaluation of such homogeneous samples of control subjects and Alzheimer subjects in whom illness has been staged allows estimation of specific minimum personality changes (27, 28), affective symptoms (29), and psychotic symptoms (30, 31) as a function of disease severity (32).

The initial purpose of enrolling subjects with a rating of 0.5 (questionable dementia) was to examine whether the mild cognitive deficits in this group represented very mild dementia of the Alzheimer type or benign changes not predictive of progressive illness. Recently, we demonstrated that 11 of the original 16 subjects with a 0.5 rating enrolled in 1979 had Alzheimer's disease verified at postmortem or had progressed to a more advanced stage in which dementia of the Alzheimer type was clearly evident in the subsequent 7-year period (33). Furthermore, two of the 58 control subjects from the 1979 sample had progressed to a 0.5 rating and subsequently died, and their autopsies verified Alzheimer's disease (34, 35). Therefore, the majority of the subjects with a rating of 0.5 can be considered as having very mild dementia of the Alzheimer type. In 1984, an additional 25 subjects with a 0.5 rating were enrolled in a second longitudinal study. In this report, we compare the personality changes, affective symptoms, and psychotic symptoms of the combined sample of 41 subjects with questionable dementia (rating of 0.5) with those occurring in control subjects and subjects with mild dementia of the Alzheimer type (rating of 1). A minority of subjects with questionable dementia may have nonprogressive, benign changes, perhaps representing "age-associated memory impairment" (36, 37), and, therefore, our estimates of psychopathology in very mild dementia of the Alzheimer type are probably low.

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TABLE 1. Personality Changes in Subjects With Questionable or Mild Dementia of the Alzheimer Type and in Control Subjects

Group	Clinical Dementia Rating	Passive		Agitated		Self-Centered		All Three		Any	
		N	%	N	%	N	%	N	%	N	%
Control (N=83)	0	0	0	4	5	4	5	0	0	8	10
Questionable dementia (N=41)	0.5	17	41[a,b]	14	34[a]	14	34[a]	5	12[a]	27	66[a]
Mild dementia (N=68)	1	48	71[a]	21	31[a]	29	43[a]	9	13[a]	57	84[a]

[a] Significantly different from control group (Fisher's exact test, $p<0.05$, Bonferroni correction).
[b] Significantly different from mild dementia group (Fisher's exact test, $p<0.05$, Bonferroni correction).

METHOD

Diagnostic criteria, subject recruitment, and descriptions of the subject groups are given in detail elsewhere (21, 23, 30, 31). In summary, the diagnostic criteria for dementia of the Alzheimer type are compatible with *DSM-III* and the NINCDS-ADRDA criteria (38). The data we present are from two longitudinal studies (the first began in 1979 and the other in 1984). In the first study, 58 control subjects (rating of 0), 16 subjects with questionable dementia (rating of 0.5), and 44 subjects with mild dementia of the Alzheimer type (rating of 1) were enrolled. In the second study, 25 control subjects, 25 subjects with questionable dementia, and 24 subjects with mild dementia were enrolled. All subjects met rigorous inclusion and exclusion criteria. All participants were between the ages of 64 and 82 years and living in the community at entry to the study. Although recruitment was not restricted by race, all participants were caucasian; control and dementia of the Alzheimer type subjects did not differ with respect to educational level or social status.

The data we report were gathered from the initial protocol in which a 90-minute, semistructured interview involving the subject and a well-informed collateral (usually a close relative) source (21, 24) is administered by a clinician (21, 24) to each subject at enrollment in the study. Information from this assessment allows the clinician to rate the dementia as absent, questionable, mild, moderate, or severe on the basis of a composite obtained from six "box scores" that evaluate memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (21, 23, 24).

Personality changes were determined from answers to open-ended questions concerning mental and physical health and to the 11 items of the Blessed-Roth Dementia Scale (39). These changes were classified into three common, clinically useful groups on the basis of an earlier study that used factor analysis techniques (28): passive changes (insecure-inactive, less cheerful, less responsive), agitated changes (irritable, hyperactive), and self-centered changes. Affective symptoms based on the Feighner criteria (40) were elicited by direct questioning of the collateral source and the subject. Psychotic symptoms, obtained from open-ended and symptom-specific questions (30, 31), were classified into three groups: delusions (most commonly involving stealing or suspiciousness), misidentification syndromes (involving the belief that people were in the house who were not, the belief that people on television were alive and in the same room, or the inability to recognize one's own face in the mirror), and hallucinations (30–32). Results were analyzed with a two-tailed Fisher's exact test.

RESULTS

There were 83 control subjects (32 men, 51 women; mean±SD age, 71.6±4.9 years); 41 subjects with questionable dementia (23 men, 18 women; mean±SD age, 73.9±5.2 years), and 68 subjects with mild dementia (31 men, 37 women; mean ±SD age, 72.1±5.0 years). The 41 subjects with questionable dementia were slightly older than the mild dementia or control subjects ($p \le 0.05$); however, the same pattern of psychiatric changes occurred in the original (1979) longitudinal study subjects with questionable dementia (N=16; eight men, eight women; mean±SD age, 71.7±4.1 years) and the 1984 longitudinal study subjects with questionable dementia (N=25; 15 men, 10 women; mean±SD age, 75.4±5.4 years).

The percent of subjects with passive, agitated, or self-centered changes is presented in table 1. Only 10% (N=8) of the control subjects showed any personality changes, whereas 66% (N=27) of the group with questionable dementia, and 84% (N=57) of the mild dementia group demonstrated behavioral changes. The pattern of personality changes seen in the group with questionable dementia more closely resembled that occurring in patients with mild dementia than in subjects without dementia.

Individual depressive symptoms, reported by the subjects and the collateral sources, are presented in table 2. More subjects with mild dementia and more with questionable dementia reported low levels of interest and concentration than control subjects. Similarly, the collateral sources for the mild dementia group reported low levels of energy, interest, and concentration, more psychomotor changes, and, to a lesser degree, more feelings of guilt and suicidal thoughts in the subjects, than did the collateral sources for the control subjects. The reports of the collateral sources for the subjects with questionable dementia indicated that these individuals had a profile of depressive symptoms similar to the mild dementia group, involving low

TABLE 2. Depressive Symptoms in Subjects With Questionable or Mild Dementia of the Alzheimer Type and in Control Subjects as Reported by Subjects and Their Collateral Sources

Source and Group	Clinical Dementia Rating	Dysphoria		Change in Appetite		Change in Sleep		Low Energy		Psychomotor Change		Low Interest[a]		Guilt		Poor Concentration		Suicidal Thoughts	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Self-report																			
Control (N=83)	0	23	28	3	4	13	16	16	19	10	12	4	7	6	7	9	11	4	5
Questionable dementia (N=41)	0.5	5	12	1	2	5	12	8	20	6	15	3	19	4	10	15	37[b]	2	5
Mild dementia (N=68)	1	19	28	7	10	8	12	17	25	7	10	12	27[b]	7	10	32	47[b]	1	2
Collateral source																			
Control (N=83)	0	9	11	3	4	11	13	10	12	3	4	0	0	1	1	1	1	1	1
Questionable dementia (N=41)	0.5	8	20	4	10	9	22	13	32[b]	8	20[b]	3	19[b]	3	7	18	44[b,c]	2	5
Mild dementia (N=68)	1	18	27	9	13	10	15	24	35[b]	18	27[b]	17	39[b]	8	12[b]	47	69[b]	10	15[b]

[a] Interest was not specifically asked about in the 1984 longitudinal study; these percents are based on the 1979 longitudinal sample only (control, N=58; questionable dementia, N=16; mild dementia, N=44).
[b] Significantly different from control group (Fisher's exact test, $p<0.05$, Bonferroni correction).
[c] Significantly different from mild dementia group (Fisher's exact test, $p<0.05$, Bonferroni correction).

TABLE 3. Psychotic Symptoms in Subjects With Questionable or Mild Dementia of the Alzheimer Type and in Control Subjects

Group	Clinical Dementia Rating	Delusions		Misidentifications		Hallucinations		Any	
		N	%	N	%	N	%	N	%
Control (N=83)	0	0	0	0	0	0	0	0	0
Questionable dementia (N=41)	0.5	1	2[a]	0	0[a]	0	0[a]	1	2[a]
Mild dementia (N=68)	1	14	21[b]	8	12[b]	9	13[b]	20	29[b]

[a] Significantly different from mild dementia group (Fisher's exact test, $p<0.05$, Bonferroni correction).
[b] Significantly different from control group (Fisher's exact test, $p<0.05$, Bonferroni correction).

levels of energy, interest, and concentration and more psychomotor changes.

The frequency of psychotic symptoms as a function of illness severity is presented in table 3. Although 29% (N=20) of the subjects with mild dementia reported one or more psychotic symptoms, only one subject in the questionable dementia group had a psychotic symptom. The questionable dementia group, therefore, more closely resembled the control group than the group with mild dementia with respect to occurrence of psychotic symptoms.

DISCUSSION

The personality changes seen in the subjects with questionable dementia were similar to those occurring in subjects with mild dementia. From these data and our previously reported results on personality changes associated with moderate and severe dementia (28, 32), we can describe the following patterns of changes. Passive changes are present in the earliest stages of dementia of the Alzheimer type and increase slightly beyond the mild stages. Agitation is also present in very mild cases and continues to increase throughout the course of dementia of the Alzheimer type, whereas self-centeredness occurs in very mild dementia of the Alzheimer type and continues to increase until the moderate stages of the illness are reached. When personality changes occur early in the course of the illness, subjects do not cognitively deteriorate faster than subjects without early personality changes (28).

In terms of depressive symptoms, more subjects with mild dementia demonstrated low levels of interest, concentration, and energy and psychomotor changes than questionable dementia and control subjects. Since none of the subjects developed a major depression during a several-year follow-up period (29, 41), these changes are probably a result of the process of dementia of the Alzheimer type and not a concurrent depression. Our questionable dementia subjects more closely resembled subjects with mild dementia of the Alzheimer type than control subjects in terms of these pseudodepressive symptoms.

The criteria used in this study excluded subjects with current or past depression. In clinical practice depression and dementia of the Alzheimer type probably coexist in a substantial minority of patients (7, 8). Because these two common diseases in the elderly have substantial symptom overlap, there is a need to develop mechanisms of separating the pseudodepressive symptoms of dementia from concurrent major affective disorder and dementia (9). In making the additional diagnosis of major depression in a patient with very mild or mild dementia of the Alzheimer type, emphasis should be placed on the psychological depressive symptoms voiced by a patient, such as dysphoria, guilt feelings, low self-esteem, and suicidal thoughts. Careful longitudinal studies of subjects who have cognitive and functional impairment together with major depressive symptoms are necessary to learn how to separate these diagnoses. The development of objective tests that highly correlate such symptoms with either depression or dementia of the Alzheimer type is needed.

Psychotic symptoms, which are common in dementia of the Alzheimer type (16–18, 30, 31), are most obvious during the moderate stages of dementia of the Alzheimer type (30). In addition, the early presence of psychotic symptoms correlates with more rapid cognitive deterioration (31, 42). Psychotic symptoms may be a marker for increased involvement of Alzheimer's disease in the temporal lobe. Unlike the personality and affective manifestations of dementia of the Alzheimer type, delusions, misidentifications, and hallucinations are almost never present until the illness is at least at a mild level; therefore, patients who have substantial psychotic symptoms and very mild cognitive deficits are likely to have illnesses other than, or in addition to, very mild dementia of the Alzheimer type.

Understanding the nature and natural history of the noncognitive, psychiatric changes of dementia of the Alzheimer type is essential when analyzing the efficacy of new treatments, whether behavioral or pharmacologic or involving transplants. Certain treatments may lead to global improvement, others may improve cognitive but not noncognitive symptoms, and others may improve certain symptoms at the expense of other symptoms. Studying the psychiatric symptoms of dementia of the Alzheimer type may help us to further understand the functional anatomy underlying these symptoms, which in turn may extend to a better understanding of the pathophysiology of such other psychiatric disorders as psychosis and personality disorders.

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Self-Defeating Personality Disorder and *DSM-III-R*: Development of the Diagnostic Criteria

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One of the major controversies during the development of DSM-III-R *was the possible inclusion of self-defeating personality disorder. The authors review the clinical literature that serves as the conceptual basis for this diagnosis. The development of the diagnostic criteria is described, including the rationale for specific criteria and the objections raised by opponents of the category. The authors describe how some of these objections led to changes in the diagnostic criteria in an attempt to distinguish self-defeating personality disorder from normal reactions to victimization and abuse.*

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The concept of masochistic personality has a long and rich clinical tradition, although papers about the disorder have been largely confined to the psychoanalytic literature. The term "masochism" was originally coined by Krafft-Ebing (1) in reference to a psychosexual disorder. Freud (2) extended the concept to include erotogenic masochism, feminine masochism, and moral masochism. The latter most clearly relates to personality functioning, describing a readiness to incur failures and accidents and to lash oneself with self-reproach. A number of descriptions of masochistic character traits have since been provided in the psychoanalytic literature, although the explanations for this behavior pattern have varied. Reich (3) described a masochistic character as displaying chronic, unfounded feelings of suffering, with annoying complaints and demands, self-abasement, provocation, self-inflicted pain, and awkward social behavior. Horney (4) suggested that masochistic character entailed two main trends. The first was a tendency toward self-minimization, which resulted in feelings of unattractiveness, helplessness, insignificance, inefficiency, and worthlessness. The second was a clinging dependency. More recent psychoanalytic descriptions of the masochistic and/or depressive-masochistic personality were provided by Asch (5), Bemporad (6), Gunderson (7), Kernberg (8), Shainess (9), and Simons (10). These more recent descriptions have included the tendency to be pessimistic, self-thwarting, self-critical, submissive, self-blaming, self-effacing, sacrificial, self-punishing, self-destructive, and unnecessarily prone to failure in a wide variety of areas.

It is, at times, assumed that the sole support for the diagnosis comes from the psychoanalytic literature. This may be due in part to the fact that most of the proponents of the diagnosis have a psychoanalytic perspective and the initially proposed title for the diagnosis ("masochistic") is from this literature. However, certain aspects of the behavior pattern have been recognized from other theoretical perspectives, under different titles, and with alternative explanations of its etiology (10, 11). Schneider (12) included a "depressive psychopath" in his influential taxonomy of personality disorders: "The basic common characteristic of depressives is the constant pessimism or at any rate their very skeptical view of life, which they seem to reject yet at the same time seem to love in a rather dismal way. Suffering is taken as a mark of quality and there is a tendency to establish an aristocracy of discomfort." Beck (13) incorporated within his cognitive model of depression the concept of masochism, including the tendency "to interpret the lack of complete

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success as failure; to have self-doubts even when successful; to magnify . . . personal defects; to react to criticism with self-abasement; and to expect rejection." Beck suggested that these persons are prone to depression as a result of a negative, self-referential cognitive schema by which they think of themselves as unworthy, incapable, and undesirable and expect failure, rejection, and dissatisfaction (14). The psychologist Murray (15) included in his formulation of 20 basic human needs the need for abasement, characterized by tendencies to submit passively to external forces; to accept injury, blame, criticism, and punishment; to become resigned to fate; and to enjoy pain, punishment, illness, and/or misfortune.

DEVELOPMENT OF THE DIAGNOSTIC CRITERIA

The diagnosis of masochistic personality was considered for inclusion in *DSM-III* only shortly before the manual went to press. The reasons for this are not entirely clear since two other personality disorders that primarily come from a psychoanalytic tradition, narcissistic and borderline, were included in *DSM-III*. Perhaps the major reason was that at the time it seemed as though a descriptive approach to defining the category would be impossible, since the psychoanalytic literature on the disorder focused primarily on psychodynamic rather than descriptive features.

With the publication of *DSM-III* in 1980, many clinicians questioned the omission of this category (7, 16). At a conference to evaluate *DSM-III* in October 1983, Simons (10) discussed the importance of the concept of masochistic personality for clinical work and for educating mental health professionals, and he called for its inclusion in the next revision of the manual.

Shortly after work began on the revision of *DSM-III* in the summer of 1983, a project was initiated to develop and test descriptive diagnostic criteria for masochistic personality disorder (17). Ten criteria based on a review of the literature (2, 18–29) were pilot tested by having clinicians rate patients selected catch-as-catch-can from their outpatient practices. Although limited by methodology (e.g., clinicians were not blind to the criterion diagnoses), the study did provide initial data on the descriptive validity of the diagnosis. The results indicated that most of the behaviors described in the criteria were common in the sample studied. In addition, the criteria had good internal consistency (Cronbach's alpha, 0.76). With only a few exceptions, each criterion had a higher correlation with the clinician's diagnosis of masochistic personality than with the clinician's scaled ratings of the existing *DSM-III* personality disorder diagnoses (17).

These criteria for masochistic personality disorder were presented at a June 4, 1984, meeting of over 30 researchers and clinicians of the Personality Disorders Advisory Committee to the Work Group to Revise *DSM-III*. Two items—"often prides self on being ethically or morally superior to others" and "often sexually excited by fantasies, stories, or pictures of being humiliated, punished, hurt, or coerced"—were eliminated on the basis of the results of the pilot study, which showed that these two items had low correlations with the clinicians' diagnoses of masochistic personality. After much discussion, the committee agreed unanimously to recommend the addition of the category to *DSM-III-R*. These nine criteria were revised and eventually published in the Oct. 5, 1985, draft of *DSM-III-R* (see appendix 1).

In the summer of 1985, the APA Committee on Women reviewed the draft of the *DSM-III-R* classification and raised the following objections to the masochistic personality category: 1) it is implicitly sex-biased and will be misapplied primarily to women, 2) it is based on discredited psychoanalytic theory and violates the *DSM-III* norm of avoiding basing diagnosis on etiologic theories, 3) it ignores the fact that our culture fosters behaviors in women that could be misinterpreted as being masochistic, 4) it describes normal responses to the experience of victimization, 5) it ignores the victim's actual experience and empowers a perhaps well-meaning but uninformed diagnostician to assume that an individual has the opportunity to get out of an abusive situation, and 6) it increases the likelihood that the victim of violence, rather than the perpetrator, will be seen as the individual with psychopathology.

A meeting was held on Nov. 18, 1985, that included members of the original Advisory Committee on Personality Disorders who had a special interest in the category of masochistic personality disorder, representatives of the APA Committee on Women, and several women suggested by the Program on Women of the American Psychological Association who had studied problems of abused women. At the meeting, there was a brief review of the advisory committee's rationale for proposing the inclusion of masochistic personality disorder in *DSM-III-R*, including the results of the initial empirical study (17). Also presented were the results of a just-completed study (30) of a larger and socioeconomically more diverse sample assessed with the criteria for masochistic personality disorder that appeared in the Oct. 5, 1985, *DSM-III-R* draft. The results of the newer study indicated that five of the nine individual items were significantly more common in women than in men.

The critics of the diagnosis noted that the findings supported their argument that the diagnosis was more commonly applied to women. Other participants noted, however, that differential sex prevalence does not by itself indicate bias (31) and that many psychiatric disorders occur more often in one sex than the other (32, 33). Proponents of the diagnosis cited a study by Fuller and Blashfield (34) that assessed sex bias in the diagnosis of masochistic personality disorder. In that study, 150 clinicians were provided with 15 case histories, five of which involved masochistic patients (three were prototypic cases and two were not). Sex was varied across case histories. The results indicated that clinicians were no more likely to diagnose masochistic personality in women than in men.

Critics of the diagnosis also objected to what they regarded as a major methodologic error in the initial empirical study (17): no data were collected about the subjects' current or past histories of being victimized or abused. According to the critics, their own studies of victimized women, primarily women who were physically abused by their husbands, indicated that the women's behavior was largely a function of their actual situations; soon after they were removed from the abusive situations, behavior that might have appeared to be "masochistic" disappeared (35). Since the victimization of women in our society is so common and so often unrecognized by clinicians, the critics of the diagnosis argued that this failure to collect data about victimization rendered the study meaningless. They also noted that in their studies of abused women, no relationship was found between measures of personality disturbance and a history of having ever been abused (36). Rosewater (37), for example, compared the MMPI scale scores of 106 women who were currently in abusive relationships with the scores of 12 women who had previously been abused. The formerly battered women had lower scores, and the scores on several MMPI scales were significantly correlated with the frequency of battering and the degree of violence, suggesting to the critics that the apparent maladaptive traits were a response to, rather than a cause of, victimization. Proponents of the diagnosis responded by indicating that many of these studies failed to include comparison groups of women who were not in abusive situations; therefore, no conclusions could be drawn about the relationship between personality and a propensity for being victimized. Proponents also stated that Rosewater's data did not take into consideration the limited value of self-report inventories, such as the MMPI, for assessing personality (38). It was also noted that only a small minority of battered women would be expected to have a distinct pattern of maladaptive personality traits (39). Finding no distinct pattern in heterogeneous samples of abused women does not reflect on the validity of the concept of masochistic personality.

Further discussion resulted in acknowledgment by proponents of the diagnosis that some of the criticisms of the diagnostic criteria for the proposed category were on target. It was also decided that the term "masochistic" should be avoided because of its historical association with controversial psychoanalytic notions about female sexuality and the implication that the "masochist" derives unconscious pleasure from suffering. A tentative alternative, "self-defeating personality disorder," was suggested by several of the proponents of the category. Each of the original criteria was then examined in light of the results of the empirical studies and the criticisms that had been offered. Most of the criteria were revised, a few were eliminated, and several new criteria were suggested.

In the several months following this meeting, the diagnostic criteria were further refined. Appendix 1 presents the nine criteria that appeared in the Oct. 5, 1985, draft of *DSM-III-R* and the final list of eight that appear in appendix A of *DSM-III-R*. Three criteria were eliminated, five were revised, and two were added. There was an attempt to word the criteria to reflect psychopathology, rather than culturally or situationally based behavior. For example, the draft item 2, "Believes that he or she almost always sacrifices own interests for those of others" was changed to "Engages in excessive self-sacrifice that is unsolicited by the intended recipients of the sacrifice (*DSM-III-R* item 8). A paragraph introducing the criteria was included so that the diagnosis will be used only in cases in which the self-defeating behaviors have been present since early adulthood and have been present in a variety of contexts. To ensure further that the diagnosis will not be used in isolated situations in which the behaviors are simply a response to an abusive situation, criterion B was added. Since self-defeating behavior can be a symptom of depression rather than a reflection of a personality disturbance, criterion C was included to rule out self-defeating behavior that occurs only when the individual is depressed.

In September 1985, the Board of Trustees appointed an ad hoc committee with members of both the Board of Trustees and the Assembly of District Branches to review the progress being made by the Work Group to Revise *DSM-III*, paying special attention to proposed revisions that were particularly controversial. On Dec. 3, 1985, this committee held a 1-day meeting to hear from proponents and opponents of this and other controversial categories that were being considered for inclusion in *DSM-III-R*. After hearing from proponents and critics of self-defeating personality disorder, the joint ad hoc committee gave tentative approval for the inclusion of the category in an appendix to *DSM-III-R* and for a national field trial that would provide data on the sensitivity and specificity of the proposed diagnostic criteria. On Dec. 7, 1985, the Board of Trustees approved the recommendations of the joint ad hoc committee but tentatively approved inclusion of self-defeating personality disorder in the body of the text rather than in an appendix, as recommended.

In June 1986, the Board of Trustees formally approved *DSM-III-R* but reversed its initial decision to include self-defeating personality disorder in the body of the manual and instead approved its inclusion (with two of the other controversial categories) in an appendix titled "Proposed Diagnostic Categories Needing Further Study."

DISCUSSION

A diagnostic classification identifies behaviors and syndromes that should be regarded as pathological. In addition, it enables clinicians to communicate about the disorders with which they deal, to facilitate the prevention and treatment of these disorders, and to comprehend the causes and processes involved in their development and maintenance (40). As stated in *DSM-III*, many factors are considered in the decision to include a new disorder in an official classification of mental disorders: clinical usefulness, reliability, acceptability to clinicians and researchers of varying theoretical orientations, usefulness for educating health professionals, and empirical support for its validity.

Justification for including the diagnosis of self-defeating personality disorder in *DSM-III-R* is lacking in some respects but is present in others. The predictive and construct validity of the diagnosis has not been established empirically, but the empirical support is comparable with that for many other disorders. It is often necessary to recommend for general use a diagnosis for which only face validity can be demonstrated (40). Proponents of the inclusion of self-defeating personality disorder in *DSM-III-R* believed that a major argument for its inclusion was its potential clinical usefulness (7, 10, 16).

There continues to be considerable interest and controversy with regard to the diagnosis of self-defeating personality disorder. The new *Journal of Personality Disorders* published a special issue devoted to the controversy surrounding the category (11, 30, 37, 41–44). Symposia at the 1987 annual meeting of the American Psychological Association were devoted to "self-defeating behaviors" and to the self-defeating personality disorder diagnosis. The *DSM-III-R* diagnostic criteria for self-defeating personality disorder have been included in four structured diagnostic interviews and a self-report instrument that assess personality disorders (45–49). The preliminary data on these instruments suggest that some of the items (e.g., incites angry or rejecting responses from others and then feels hurt, defeated, or humiliated) may be difficult to assess reliably and need further revision.

Future research should address the following questions: Is the diagnosis more often incorrectly applied to women than men? Is the diagnosis stable over time, as would be predicted, or is it made primarily during periods of stress, depression, or victimization? Are there specific developmental antecedents of the disorder, such as a history of child abuse? Is self-defeating personality disorder a unique personality disorder or merely a dimension of personality disturbance that coexists with a variety of other personality disorders? Does the diagnosis predict specific patient behavior in treatment and the need to employ certain specific treatment strategies? Answers to these questions would facilitate an informed decision about the value of including the diagnosis in *DSM-IV*.

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APPENDIX 1. Draft and Final *DSM-III-R* Criteria for Self-Defeating Personality Disorder

OCT. 5, 1985, DRAFT (Masochistic Personality Disorder)

Feelings of martyrdom and self-defeating behavior as indicated by at least six of the following:

(1) Remains in relationships in which others exploit, abuse or take advantage of him or her, despite opportunities to alter the situation

(2) Believes that he or she almost always sacrifices own interests for those of others

(3) Rejects help, gifts or favors so as not to be a burden on others

(4) Complains, directly or indirectly, about being unappreciated

(5) Responds to success or positive events by feeling undeserving or worrying excessively about not being able to measure up to new responsibilities

(6) Always pessimistic about the future and preoccupied with the worst aspects of the past and present [eliminated]

(7) Thinks only about his or her worst features and ignores positive features [eliminated]

(8) Sabotages his or her own intended goals

(9) Repeatedly turns down opportunities for pleasure

DSM-III-R

A. A pervasive pattern of self-defeating behavior, beginning by early adulthood and present in a variety of contexts. The person may often avoid or undermine pleasurable experiences, be drawn to situations or relationships in which he or she will suffer, and prevent others from helping him or her, as indicated by at least five of the following:

(1) Chooses people and situations that lead to disappointment, failure, or mistreatment even when better options are clearly available [see draft item 1]

(2) Rejects or renders ineffective the attempts of others to help him or her [see draft item 3]

(3) Following positive personal events (e.g., new achievement), responds with depression, guilt, or a behavior that produces pain (e.g., an accident) [see draft item 5]

(4) Incites angry or rejecting responses from others and then feels hurt, defeated, or humiliated (e.g., makes fun of spouse in public, provoking an angry retort, then feels devastated) [new criterion]

(5) Rejects opportunities for pleasure, or is reluctant to acknowledge enjoying himself or herself (despite having adequate social skills and the capacity for pleasure) [see draft item 9]

(6) Fails to accomplish tasks crucial to his or her personal objectives despite demonstrated ability to do so, e.g., helps fellow students write papers, but is unable to write his or her own [see draft item 8]

(7) Is uninterested in or rejects people who consistently treat him or her well, e.g., is unattracted to caring sexual partners [new criterion]

(8) Engages in excessive self-sacrifice that is unsolicited by the intended recipients of the sacrifice [see draft item 2]

B. The behaviors in A do not occur exclusively in response to, or in anticipation of, being physically, sexually, or psychologically abused.

C. The behaviors in A do not occur only when the person is depressed.

Defense Mechanisms in Risk of Suicide and Risk of Violence

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This paper reports on an empirical study of defense mechanisms in 60 psychiatric inpatients. Eight defenses—compensation, denial, displacement, intellectualization, projection, reaction formation, regression, and repression—were studied in the context of a two-stage model of suicidal and violent behavior. The results showed that use of regression as a defense differentiated suicidal from nonsuicidal patients, and use of displacement differentiated violent from nonviolent patients. Repression tended to turn aggression inward, and projection and denial turned aggression outward.
(Am J Psychiatry 1989; 146:1027–1031)

The concept of ego defenses is among the more important contributions of psychoanalysis to personality theory and to the theory of psychological adaptation. From a psychoanalytic point of view, ego mechanisms of defense are mental processes that attempt to resolve conflicts among drive states, affects, and external reality. According to Vaillant (1), defense mechanisms moderate levels of emotion produced by stress, they help keep awareness of certain drives at a minimum, they provide time to help an individual deal with life traumas, and they help deal with unresolvable loss. Despite the wide acceptance of the concept of defense mechanisms and despite their extensive use in the clinical context, there has not been much empirical research using the concept of defense mechanisms because of the lack of a reliable and valid method for measuring the extent to which individuals use the different defenses (2). Some attempts have been made to develop such instruments (2–9); however, none of the various instruments devised for studying defenses has been widely used in clinical research in general or in research on suicide in particular.

Psychodynamic theories of suicide have, of course, extensively discussed the role of defense mechanisms. Freud (10) assumed that loss was the basis of depression. To defend against the loss and the anger felt against the person who has been lost, the mental representation (object) of that person is introjected. The hostility felt toward the lost object is first repressed and then becomes turned against the self. The defenses involved in suicide include introjection, incorporation, identification, ego splitting, and regression (11).

Surprisingly, there have been few attempts to use empirical methods in the study of the defense mechanisms of violent and suicidal patients. Scholz (12) used the Defense Mechanism Inventory to evaluate the defenses of 35 suicide attempters. His results supported psychoanalytic theory in that the suicidal subjects showed more turning against the self than did the control subjects.

Pfeffer et al. (13) reviewed a series of empirical studies that she and her colleagues had done on ego defense mechanisms in suicidal children. They had evaluated 11 defenses and reported that introjection was significantly more common in suicidal children than in nonsuicidal children. They related this finding to the severe separation-individuation problems experienced by suicidal children and stressed the role of splitting as a fundamental defense mechanism of last resort in these children. Pfeffer et al. (13) also examined defenses in relation to assaultive behavior of children and found that compensation, projection, and displacement were the most highly correlated with such behavior.

On the basis of a review of the literature and some empirical studies, Plutchik et al. (14) proposed a two-stage vectorial model of suicidal and violent behaviors that is similar to some of the classic psychoanalytic

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theories we have just described. An aggressive drive or impulse, activated by a trigger, is acted upon by a variety of psychosocial, psychological, and biological variables that initially either augment or attenuate the drive. Then, a new set of variables act on the drive and influence its direction, either inward or outward. Suicidal or violent behavior can thus be conceptualized as the vectorial result of competing sets of forces. This model makes explicit the widespread belief that outward aggression and suicide are interrelated both psychodynamically and socially.

The present study was an attempt to provide additional evidence for this model; we report on the correlations between measures of defenses, emotions, and risks of suicide and violence. The study was part of a long-term project evaluating the role of various psychometric and biological variables in suicidal and violent psychiatric patients.

METHOD

Sixty patients on the inpatient wards of the Bronx Municipal Hospital Center were interviewed and tested. The interviews took place within 10 days of the patients' admission to the inpatient service. All patients who were willing to participate and whose therapists agreed to their participation were eligible for the study, with the exception of those under 18 or over 64 years of age, those with organic syndromes, and those who lacked fluency in English. All participating patients signed consent forms. No attempt was made to select any particular diagnostic category of patients, since clinical experience indicates that patients of all diagnostic types are at risk for suicide or violence or both. A review article has documented this point in regard to suicide (15).

Initially, patients were selected for the study if the reason for admission was a suicide attempt. For each such patient a nonsuicidal control patient, matched according to sex, age, and diagnosis, was selected. Thus, the study eventually included 30 patients who had been admitted because of suicide attempts and 30 patients who had been admitted for other reasons. There were 15 men and 15 women in each group. In addition, follow-up on the ward indicated that 20 patients had to be secluded or restrained for assaulting a staff member or a fellow patient. This group was compared to the group of patients who were not violent on the ward. Only two of the violent patients had not been admitted because of suicide attempts.

An experienced psychiatrist interviewed each patient about the reason for his or her admission and the events leading up to the suicidal or violent event. Patients were then placed in one of three broad diagnostic categories: schizophrenic spectrum disorders, affective disorders of all types, and personality disorders of all types. We used this oversimplification in order to make an approximate comparison of the groups with respect to diagnostic distribution and to simplify the problem of matching.

A battery of self-report test measures was administered. The psychiatrist was present with the patient at all times and, if requested, would read the questions aloud and record the patient's answers.

Tests for Outcome Variables

The risk of suicide was assessed by the Suicide Risk Scale, which consists of 26 items answered yes or no by the patient. The scale includes items on past history of suicide attempts, present strength of suicidal impulses, feelings of depression and hopelessness, and other items that have been reported to be associated with patients who have made suicide attempts, such as frequent use of tranquilizers, sleeping pills, and medications of all types.

The internal reliability of the scale, based on Cronbach's coefficient alpha, has been found to be 0.84, indicating high intercorrelations among the items. The scale has been given to psychiatric outpatients and inpatients. It correlates with clinicians' judgments of suicide risk in patients and is one of the better predictors of the beneficial effects of outpatient psychotherapy. Scores on the Suicide Risk Scale have discriminated between a group of outpatients clinically evaluated as having suicidal symptoms and a group of patients who had no suicidal symptoms and between inpatients who had made suicide attempts in the past and those who had never made such attempts (14, 16, 17).

The risk of violence was assessed by the Past Feelings and Acts of Violence Scale, which consists of 12 items answered on a 3-point scale of frequency. The patient is asked about acts of violence against others, the carrying and use of weapons, arrests, and loss of temper. The internal reliability (coefficient alpha) of the scale is 0.77, indicating high correlations among the items. The scale (in a slightly longer version) has been given to hundreds of individuals representing diverse groups: college students, pain patients, patients with epilepsy, self-referred violent patients, and prisoners. The results show that the scale clearly discriminates between most of the groups with respect to average level of expressed violence; prisoners and self-referred violent patients score highest and patients with epilepsy lowest (18). In a study of psychiatric inpatients (14, 17), scale scores significantly discriminated between patients who reported violent acts toward others and a group of patients who reported neither suicidal nor violent acts. The scale has also been used in the study of neuropsychiatric patients and to identify subgroups of violent behaviors (19).

Tests for Predictor Variables

Ego defense mechanisms were measured by the Life Style Index (20). This self-report form has 97 items and measures eight defenses: compensation, denial, displacement, intellectualization, projection, reaction formation, regression, and repression. Scores are given as percentiles based on scores of a normative group of college students. Use of the index in a number of studies has been described by Plutchik (21).

Impulsivity was measured by the Impulsivity Scale, which consists of 15 items, answered on a 3-point frequency scale, concerning the tendency to engage in impulsive, spur-of-the-moment behaviors, all of which reflect possible loss of control. The scale has a coefficient alpha of 0.79 for internal reliability, indicating high intercorrelation among items; it has been used in previous research (14, 17).

Anxiety was measured by the Spielberger State-Trait Anxiety Scale (22), which has been widely used in psychometric research. It consists of two forms, one relating to the subject's present feelings (state anxiety) and the other relating to chronic, long-term anxiety (trait anxiety).

Anger was assessed by the Multidimensional Anger Inventory (23); mood was measured by the Mood Adjective Checklist (21), which measures eight mood constellations; and life stresses were measured by the Problem Checklist (24), which quantifies seven types of life stresses.

Data Analysis

The group of 30 patients admitted for attempted suicide was compared on all test measures with the nonsuicidal control patients by means of t tests. This procedure was repeated comparing the violent group of patients with the nonviolent control patients. The Bonferroni correction was applied because of the number of tests of significance that were carried out, and two-tailed tests were always used.

We used Pearson product-moment coefficients to correlate the results of all test measures with those of the two outcome measures, risk of suicide and risk of violence. The test measures were then correlated with each outcome measure separately after partialing out the other outcome measure. This was done because previous research has shown that risk of violence and risk of suicide are highly intercorrelated (14). This technique enables us to know how much of a specific variable's correlation with risk of suicide is due to risk of violence, and vice versa. Again, the Bonferroni correction was applied.

RESULTS

As expected on the basis of the selection and matching procedures, there were no differences between the suicidal and nonsuicidal patients in age (mean±SD=29.8±8.6 years and 32.5±10.7 years, respectively), in sex distribution (15 men and 15 women in each group), and in broad diagnostic categories (seven with affective disorders, six with schizophrenic spectrum disorders, and 17 with personality disorders in each group). There were no significant differences between violent and nonviolent patients in age or in broad diagnostic categories. In terms of sex distribution, there were equal numbers of women in the violent and nonviolent groups (20 and 20) but more than twice as many men in the violent group (14 versus six).

The suicidal and nonsuicidal patients were compared on risk of suicide and risk of violence as well as on the eight ego defenses. Two of the measures showed a significant difference between these groups. Scores on the Suicide Risk Scale distinguished between the groups ($t=4.93$, $df=58$, $p<0.001$). Since the patients were selected as suicidal or not on the basis of their clinical histories, this finding provides some degree of external validation for the scale. The suicidal patients also scored significantly higher on regression ($t=2.61$, $df=58$, $p<0.01$).

When we compared the violent and nonviolent groups, we found four significant differences. The measure for risk of violence distinguished the two groups ($t=3.92$, $df=58$, $p<0.001$), thus providing further evidence of its validity. The violent group also scored significantly higher on displacement than the nonviolent group ($t=2.96$, $df=58$, $p<0.01$). There was also a significant tendency for the violent patients to score higher on suicide risk ($t=2.71$, $df=58$, $p<0.01$) and to score lower on reaction formation ($t=2.64$, $df=58$, $p<0.01$).

Since we found that risk of violence and risk of suicide are highly correlated ($r=0.62$), we present the partial correlations also. On the basis of our two-stage model of countervailing force, which was the theoretical basis for the study, it would be expected that the variables which showed significant partial correlations with the measures for both risk of suicide and risk of violence would act as stage 1 amplifiers or attenuators of the aggressive impulse. It would be assumed that the variables which showed significant correlations only with risk of violence or only with risk of suicide act primarily as determinants of the direction of the aggressive impulse (to self or other).

Table 1 presents the total and partial correlations of scores on the eight defense mechanisms with scores on risk of suicide and risk of violence. The Bonferroni correction indicated that correlations over approximately 0.32 were significant. Examination of table 1 reveals that three variables were significant partial correlates of risk of suicide, and two variables were significant partial correlates of risk of violence. Patients who scored high on the use of repression as a defense had a high risk of suicide (0.47) and a low risk of violence (−0.31). Patients who scored high on displacement had a high risk of suicide (0.34) and a positive but not significant tendency to be violent (0.25). Patients with high scores on denial had a low risk of suicide (−0.51) and a high risk of violence (0.32). The use of projection as a defense was not significantly correlated with risk of suicide (0.13) but was highly correlated with risk of violence (0.46).

TABLE 1. Correlations of Defense Mechanisms With Risk of Suicide and Risk of Violence in 60 Psychiatric Patients[a]

Defense Mechanism	Risk of Suicide		Risk of Suicide With Risk of Violence Partialed Out		Risk of Violence		Risk of Violence With Risk of Suicide Partialed Out	
	r (df=58)	p	r (df=58)	p	r (df=58)	p	r (df=58)	p
Regression	0.48	<0.001	0.26	n.s.	0.48	<0.001	0.27	n.s.
Displacement	0.47	<0.001	0.34	<0.01	0.46	<0.001	0.25	n.s.
Repression	0.27	n.s.	0.47	<0.001	−0.48	<0.001	−0.31	n.s.
Projection	0.25	n.s.	0.13	n.s.	0.26	n.s.	0.46	<0.001
Compensation	0.25	n.s.	0.00	n.s.	0.31	<0.01	0.25	n.s.
Intellectualization	0.18	n.s.	−0.23	n.s.	0.19	n.s.	0.30	n.s.
Reaction formation	−0.10	n.s.	−0.03	n.s.	−0.23	n.s.	0.15	n.s.
Denial	−0.42	<0.001	−0.51	<0.001	−0.03	n.s.	0.32	<0.01

[a] See text for measures of defense mechanisms and risks of suicide and violence.

DISCUSSION

The fact that regression was significantly higher in the suicidal patients than in the nonsuicidal patients is consistent with the clinical observation that suicidal patients have greater potential for severe infantile acting out behavior than do nonsuicidal patients. In addition, in this and in a previous study (14), the suicidal patients had significantly higher numbers of life problems, indicating that they had been under more severe stress before admission. This greater stress may itself have produced more regressive behavior, one aspect of which included the suicide attempt. Certainly, the clinical impression given by this particular group of suicidal patients was that their suicidal behavior was more a product of impulsive acting out in the face of intolerable life stress than of well-thought-out, planned decisions to kill themselves.

The fact that displacement was more marked in the violent patients confirms the clinical impression that many acts of violence represent displacement of aggression from primary objects onto symbolic representations of or substitutes for those objects.

The correlations of the defenses with suicide and violence reveal that repression plays a significant but differential role in suicide and violent behavior. Repression had the highest positive correlation with risk of suicide and, thus, in terms of the two-stage vectorial theory that we have proposed, may be considered an important mechanism by which aggressive drive is turned inward. This view is supported by the significant negative correlation between repression and risk of violence.

Interestingly, denial appears to act almost exactly opposite to repression in this regard. Denial had the most negative correlation with risk of suicide and a significant positive correlation with risk of violence. Thus, the effect of denial as a defense seems to be to direct the aggressive drive outward. This implies that the realistic assessment of reality and life stresses inclines one to possible depression and suicidal ideas (25), whereas denial of reality encourages the acting out of aggressive impulses. These observations are consistent with the clinical fact that delinquent youths have high rates of violent behavior (26); they also show little repression and much denial.

Dorpat (27) has described denial as a defense against anxiety and other painful affects. He pointed out that denial has been found to be correlated with greater survival in acute coronary patients (28). It is also associated with a lesser likelihood of suicidal thinking in manic patients (29). The results of the present study support the hypothesis that anxiety acts as an inhibitor of action and that, therefore, high anxiety (presumably associated with high denial) correlates with low risk of suicide.

The finding that projection had the highest positive correlation with risk of violence is not unexpected, since this defense is used to shift unacceptable aggressive feelings away from the self and to attribute them to other people in the environment. Indeed, projection and denial may be part of a constellation of defenses around splitting associated with intense rage (30), and repression may be the center of a defensive constellation associated with guilt. This notion is supported by the finding that anger was the emotion most highly correlated with risk of violence ($r=0.62$), whereas anxiety was the emotion most highly correlated with risk of suicide ($r=0.67$).

In conclusion, it seems that defense mechanisms are an integral part of the chain of events involved in the development of both violent and suicidal behaviors and that they act differentially and specifically. Thus, we have shown that regression and displacement augment the intensity of the aggressive drive in the first stage of the vectorial interaction. At the second stage, repression tends to direct the aggression toward the self, while projection and denial tend to direct the aggression outward. The ability to actually quantify the role of defense mechanisms in this regard and to relate their functions to other psychological and biological measures may have important implications for management of patients and for future research.

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The UCLA-University of Utah Epidemiologic Survey of Autism: Recurrence Risk Estimates and Genetic Counseling

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The authors recently reported, in this journal, an epidemiologic survey of autism in Utah. Twenty (9.7%) of the 207 families ascertained had more than one autistic child. Analyses of these data revealed that autism is 215 times more frequent among the siblings of autistic patients than in the general population. The overall recurrence risk estimate (the chance that each sibling born after an autistic child will develop autism) is 8.6%. If the first autistic child is a male the recurrence risk estimate is 7%, and if a female 14.5%. These new recurrence risk estimates should be made available to all individuals who have autistic children and are interested in family planning.

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A consensus has been reached over the past two decades by investigators throughout the world concerning autism (1, 2). It is now recognized as a specific behaviorally defined syndrome that produces irregularities in development and characteristic disturbances in relatedness, language, and responses to sensory stimuli (3). Symptoms are usually manifested before 30 months of age and are expressive of CNS dysfunction rather than psychological trauma, as was formerly thought. Most likely, more than one etiological factor and pathological process will be found that can produce the syndrome. In two-thirds of the patients, brain dysfunction is so extensive that they score in the mentally retarded ranges on standard IQ scales (4). The vast majority of patients require lifelong supervision and social support. However, mild cases occur, and some of these patients can live independently, marry, and become parents (5).

While no specific pathognomonic signs or CNS pathology is known, biomedical findings have been reported that characterize subgroups of patients. These findings include hyperserotonemia (6); decreased b-wave amplitude in the electroretinogram (7); decreased post-rotatory nystagmus (8); decreased cerebellar Purkinje cells at autopsy (9); nonspecific abnormal EEGs, MRIs, CT scans, pneumoencephalograms, and autopsy findings (3, 10); and possible cerebellar abnormalities as seen on MRI (11, 12). Autism is also known to occur in association with other diseases (2, 3).

Prior epidemiologic surveys estimated the prevalence of autism to be between 2 and 21 per 10,000 in the general population and the sibling risk to be 2% (10). Although these surveys were based on relatively small populations and used different ascertainment techniques, diagnostic criteria, and methods, the latter figure is widely quoted and cited in *DSM-III*. It indicates that siblings of autistic children have a 50-fold higher risk of autism than the general population. While risks are most often based on the total number of siblings of an affected individual, it is also useful to estimate the recurrence risk, which is based only on the siblings born after the first affected individual in each sibship. This compensates for those couples who limit reproduction after the birth of an affected child (13) (a phenomenon called stoppage). For comparability with previous studies, we report a sibling risk that is based on the total number of siblings of autistic subjects. In addition, we report recurrence risks that are based on the siblings born after the first autistic subject in each sibship. To our knowledge, recurrence risks estimated in the latter fashion have not previously been reported for autism. In only one survey to date have the siblings of autistic probands been given psychiatric examinations. Baird and August (14) diagnosed as autistic three (5.9%) of 51 siblings of 29 probands; they did not evaluate the parents.

In order to provide a more accurate and comprehensive database to explore these and related issues, we

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conducted an epidemiologic survey of autism in the state of Utah. On the basis of the survey, the best estimate for the prevalence of autism is 4 per 10,000 in the general population, and the sex ratio is 4 males to 1 female (15).

In this report we present the data on multiple-incidence families from the survey and recurrence risk estimates. These findings provide new guidelines for genetic counseling of families with autistic children. The overall recurrence risk for autism is 8.6%, and it varies with the sex of the firstborn autistic child—7.0% if a male and 14.5% if a female. The sibling risk for autism is 4.5%.

METHOD

Our recent epidemiologic survey of autism in the state of Utah (15) employed a four-level ascertainment system, *DSM-III* criteria, and a team of highly experienced clinicians who conducted blind diagnostic evaluations throughout the state. A total of 489 possibly autistic individuals born between 1960 and 1984 and living in Utah during the survey (1984–1988) were ascertained, and 241 were diagnosed as autistic. They came from 187 single-incidence families and 20 multiple-incidence families. The latter contained a total of 46 autistic siblings. Genetic research shows no excess of inbreeding or consanguinity in Utah, and the gene pool is fully representative of North American and European Caucasian populations (16, 17).

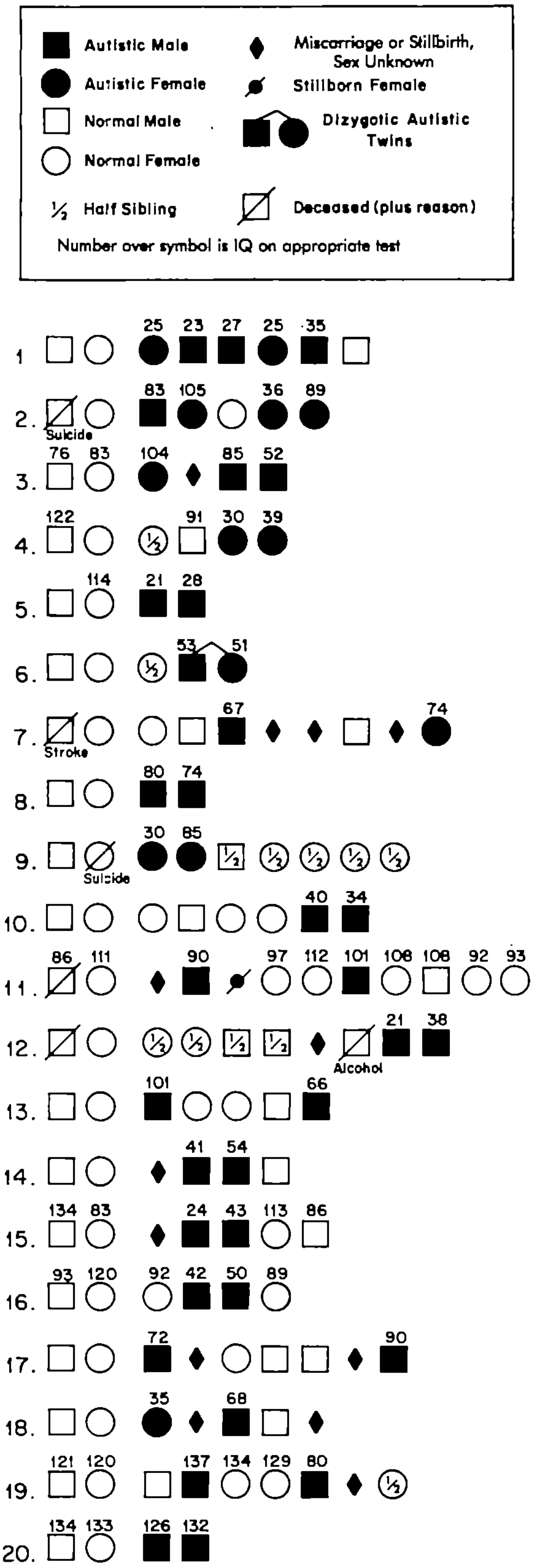
For the purposes of this study we defined sibling risk as the number of autistic siblings of the firstborn autistic child divided by the total number of siblings of the firstborn autistic child or, stated differently, the percentage of all the firstborn autistic child's siblings who are themselves autistic. Recurrence risk was determined by the later sibling method (13). This is the number of autistic siblings born after the first autistic child divided by the total number of siblings born after the first autistic child. In multiple-incidence families it is the number of autistic siblings born after the second autistic sibling divided by all siblings born after the second autistic sibling.

RESULTS

Figure 1 shows the birth order and IQ scores of first-degree relatives in the 20 multiple-incidence families identified in the survey.

Because 70% of the population of Utah identify themselves as practicing the Mormon religion, separate analyses were conducted to determine if this factor influenced the distribution and prevalence of autism. No influence was found except for larger family size, which is common for members of this religion (18). Table 1 shows family sizes and sex ratios among Mormons and non-Mormons. The mean number of siblings per family was greatest when both parents were

FIGURE 1. Birth Order and IQs of Autistic Probands and Their Siblings in 20 Families With Multiple Incidences of Autism in Utah Survey[a]



[a]The first two symbols on the left of each family represent the parents.

TABLE 1. Family Sizes and Sex Ratios in Mormon and Non-Mormon Families in Utah Survey

Item	All Families	Both Parents Mormons	One Parent Mormon	Non-Mormons
Family factors				
Siblings	787	620	54	113
Nonautistic	554	453	36	65
Autistic	233	167	18	48
Families	207	144	18	45
Siblings per family	3.80	4.31	3.00	2.51
Sex of siblings				
Nonautistic siblings				
Male	271	222	18	31
Female	283	231	18	34
Sex ratio	0.96	0.96	1.0	0.91
Autistic siblings				
Male	184	127	18	39
Female	49	40	0	9
Sex ratio	3.76	3.18	—	4.33

TABLE 2. Family Sizes, Sex Ratios, and IQs in Families With Single and Multiple Incidences of Autism in Utah Survey

Item	All Families	Single-Incidence Families	Multiple-Incidence Families
Family factors			
Siblings	787	709	78
Nonautistic	554	522	32
Autistic	233	187	46
Families	207	187	20
Siblings per family	3.80	3.79	3.90
Sex of siblings			
Nonautistic siblings			
Male	271	256	15
Female	283	266	17
Sex ratio	0.96	0.96	0.88
Autistic siblings			
Male	184	151	33
Female	49	36	13
Sex ratio	3.76	4.19	2.54
IQ and sex of siblings			
>70			
Male	67	54	13
Female	10	5	5
Sex ratio	6.70	10.80	2.60
50–69			
Male	46	39	7
Female	12	11	1
Sex ratio	3.83	3.55	7.0
<50			
Male	69	56	13
Female	26	19	7
Sex ratio	2.65	2.95	1.86

Mormon (4.31 siblings), less when only one parent was (3.0 siblings), and smallest when neither parent was (2.51 siblings). The male to female sex ratio of nonautistic siblings was approximately equal in Mormon (0.96) and non-Mormon (0.91) families. The autistic male to female sex ratio was lower in Mormon (3.18, 23.9% female) than non-Mormon (4.33, 18.8% female) families, but this difference was not significant (χ^2=0.55, df=1, p>0.10).

Table 2 shows the distribution of family sizes, sex ratios, and IQ scores in the single-incidence and multiple-incidence groups. The mean number of siblings was approximately equal in both single-incidence and multiple-incidence families (3.79 versus 3.90 siblings). The sex ratio of the nonautistic siblings was also approximately equal in both groups (0.96 for single-incidence and 0.88 for multiple-incidence families). The sex ratio of autistic siblings was lower in the multiple-incidence group than in the single-incidence group (2.54, 28.3% female versus 4.19, 19.3% female). Unfortunately, there were too few females (N=13) in the multiple-incidence group to permit clinically meaningful statistical analyses of these data. However, the intergroup difference in sex ratio of autistic siblings warrants further study when larger populations are available.

The birth order of autistic children was determined separately for sibships of size 2 and for sibships of size 3 or more (see table 3). In sibships of size 2 there was a significant tendency for autistic children to be firstborn in Mormon families, non-Mormon families, and in all the families combined. In informative sibships of size 3 or larger there was a nonsignificant tendency in the non-Mormon families for autistic children to be born later but no such tendency in the Mormon families.

Table 4 shows the proportion of multiple-incidence families and recurrence risk estimates. The overall recurrence risk was 8.6%; it indicates that siblings born after one autistic child were 215 times more likely to have autism than siblings of nonautistic children (the rate in the general population is 4 per 10,000). The sibling risk was 4.5% (95% confidence limits=2.8%–6.2%). The 95% confidence limits for recurrence risk and sibling risk indicate that the two do not differ significantly.

The recurrence risk in the informative multiple-incidence families was 35.3%, which indicates that siblings born after two autistic children are 883 times more likely to have autism than are siblings of nonautistic children. This is an approximate figure, since it is based on only eight informative families in which 17 siblings were born after the second autistic child (figure 1, families 1–3, 11, 14–16, 18). Furthermore, it could be higher because it is possible that six fathers (figure 1, families 1, 3, 7, 11, 13, 19) may be autistic adults (5).

Recurrence risks were also determined for families in which the firstborn autistic child was a male and in which it was a female. This was done to assess the hypothesis that families with firstborn autistic females are more likely to have a proposed familial form of autism, an assumption we have previously discussed and employed to divide data for analyses, e.g., a threshold polygenic model in which the female threshold is higher than that of the males (19–21). The results indicate that families in which the firstborn is an

TABLE 3. Birth Order of Autistic Children in Informative Sibships of Size 2 and Size 3 or More in Utah Survey

	All Families				Mormon Families				Non-Mormon Families				Families With One Mormon Parent			
Item	N	%	p	Z	N	%	p	Z	N	%	p	Z	N	%	p	Z
Two-child sibships	28	—	—	—	15	—	—	—	8	—	—	—	5	—	—	—
Firstborn	22	79	<0.001[a]		11	73	0.06[a]		7	88	0.04[a]		4	80	0.19[a]	
Secondborn	6	21	—	—	4	27	—	—	1	12	—	—	1	20	—	—
Sibships of three or more	153	—	>0.27[b]	0.60	121	—	>0.49[b]	0.01	22	—	>0.18[b]	0.88	10	—	>0.18[b]	0.89

[a] Binomial probability test.

[b] One-tailed, partial Mann-Whitney U test.

TABLE 4. Recurrence Risk Estimates[a] of Autism in Families in Utah Survey (Later Sibling Method)

		Proportion of Multiple-Incidence Families			Recurrence Risk			
		Multiple-Incidence Families						
Family Category	Total Families	N	%	95% Confidence Limits	All Siblings Born After Proband	Autistic Siblings Born After Proband	Recurrence Risk Estimate	95% Confidence Limits
All	207	20	9.7	6.0–14.5	302	26	8.6	5.8–12.2
With male firstborn autistic child	166	15	9.0	5.2–14.4	236.5[b]	16.5	7.0	4.3–11.2
With female firstborn autistic child	41	5	12.2	2.2–22.2	65.5[b]	9.5	14.5	6.7–24.7
Multiple-incidence families	—	—	—	—	17[c]	6	35.3	12.6–58.0

[a] Estimates based on 241 diagnosed autistic children less eight (two with fragile X chromosome, five adopted, and one with no family information), yielding 233 autistic children from 207 families; 233 total autistic children less 46 from multiple-incidence families yields 187 autistic probands from single-incidence families, plus 20 multiple-incidence families yields a total of 207 families.

[b] Includes firstborn concordant twin autistic child, who is counted as one-half.

[c] Seventeen siblings born after the second autistic child.

autistic female have a nonsignificant higher recurrence risk (14.5% versus 7.0%, $\chi^2=2.8$, df=1, p>0.10).

DISCUSSION

The overall recurrence risk of 8.6% indicates that autism is 215 times more frequent among siblings born after an autistic child than in the general population and has great clinical significance and implications for genetic counseling. It is consistent with data from our prior studies of twins (20) and multiple-incidence families (21) which indicate that there may be a subtype of autism that is genetically influenced. In addition, we found by assessing parents as well as siblings of probands in our Utah population that autism does not aggregate in families with cognitive processing pathology (22). This lends support to the corollary hypothesis that there may be genetic influences unique to autism, rather than to the notion that autism is on the extreme end of a continuum of inherited cognitive processing pathology, as has been suggested by Bartak et al. (23).

The findings on birth order show a significant trend in sibships of size 2 for the autistic child to be firstborn but no such relationship in larger sibships. This is consistent with a recently published reanalysis by one of us (M.B.J.) (13) of our earlier data derived from a nationally solicited survey of multiple-incidence families (21). That reanalysis demonstrated that families with autism tend to stop having children after the birth of an affected child, providing that child is not the firstborn. This phenomenon, referred to as stoppage, must be accounted for when determining recurrence risks and when testing models of inheritance, as we have previously discussed (20, 21).

Comparing our results to those of prior studies reveals interesting differences. While the sibling risk cited in *DSM-III* is 2%, we found it to be 4.5%. This difference may reflect our having conducted the most extensive survey to date and our having selected a large population ideally suited for epidemiological research. The recurrence risk of 8.6% is larger still. The later sibling method factors out possible effects of stoppage, which, although slight in our study, have been shown to operate in families of autistic children (13).

At this time the combined evidence for a genetically influenced type or types of autism does not precisely fit a specific mode of Mendelian inheritance. Data from previous studies (20, 21) (see references 2, 3, and 10 for review) suggest that autosomal inheritance is a possibility for one subtype. Even granting this assumption, however, we are still left with the question of what proportion of autistic patients has the proposed genetic type. As with any disease, patients with autism too mild to be diagnosed or too severe to survive or to be diagnosed cannot be identified, thus making estimates for determining possible genetic modes of transmission from clinical data alone quite imprecise. Only when the autistic phenotype or genotype can be specified with biomedical markers will we be better able to determine prevalence, recurrence risks, and modes of genetic transmission (24).

On the basis of the data presented in this report, we are counseling parents of our autistic patients that if they have another child, there is an overall 8.6% chance of having another autistic child (7% if they already have an autistic boy, 14.5% if they already have an autistic girl, and 35% if they already have two autistic children). We present this information as being preliminary and take pains to carefully explain the limited data upon which our estimates are based.

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Abnormal Melatonin Response to 5-Methoxypsoralen in Dementia

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The authors investigated the melatonin response to 5-methoxypsoralen in 39 healthy adult and elderly subjects and in 13 demented, 13 depressed, and 13 schizophrenic inpatients. Subjects' plasma melatonin levels were evaluated before they took single, oral 40-mg doses of 5-methoxypsoralen and 3 hours afterward. The preliminary results indicate that the melatonin response of the pineal gland to 5-methoxypsoralen is reduced in demented patients compared to that in healthy elderly subjects. Depressed and schizophrenic patients had a normal melatonin response to the drug. This finding suggests that the pineal gland may be functionally impaired in dementia but not in depression.

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The pineal gland hormone melatonin has recently been proved to be a valuable research tool in psychiatry. In depressive disorders, there is an indication of reduced nocturnal secretion of melatonin (1–4). This abnormally low nocturnal secretion tends to disappear during clinical remission (3). On the other hand, manic-depressive patients have been shown to be supersensitive to the inhibiting effect of bright light on nocturnal melatonin production (5). Preliminary data (6) also suggest that melatonin secretion may be severely impaired in patients suffering from Alzheimer's disease. The pineal gland is now considered to be a neuroendocrine transducer organ involved in different physiological functions such as reproduction (7), thermoregulation (8), immune response (9), and synchronization of the circadian system (10). Therefore, it seemed of great interest to investigate its functional responsiveness in different psychiatric conditions.

Administration of β-adrenergic agonists, at a limited dosage to avoid untoward cardiovascular effects, failed to increase melatonin secretion in humans whatever the timing of administration (11). Recently, we found that 5-methoxypsoralen, a furocoumarin used in dermatology for its photosensitizing properties (12), was able to induce a slow but dramatic surge of melatonin after either morning or evening administration in humans (13). The purpose of this study was thus to investigate pineal reactivity to 5-methoxypsoralen in various psychiatric conditions.

METHOD

Six groups of consecutively admitted subjects were investigated at the clinical center of the department of psychiatry of the University of Nice. Control groups 1, 2, and 3 comprised, respectively, 13 healthy elderly subjects (seven female and six male), 13 healthy middle-aged adults (seven female and six male), and 13 healthy young adults (six female and seven male). These subjects were mainly patients referred for social problems or minor neurotic reactions who had no severe psychiatric or medical illness. Most of the elderly control patients were awaiting transfer to a home for retired persons. Group 4 comprised 13 elderly inpatients (seven female and six male) who met the *DSM-III* criteria for primary degenerative dementia. Patients with dementia were excluded from the study if they showed clinical evidence of multi-infarct dementia. All the elderly patients were free from evidence of major heart, liver, kidney, endocrine, or bone disease as well as any obvious evolving pathological condition. Group 5 comprised 13 acutely depressed inpatients (eight female and five male) who met the *DSM-III* criteria for major depression. Group 6 comprised 13 schizophrenic (six female and seven male) patients diagnosed according to *DSM-III* criteria. The diagnoses were based on a structured interview for affective disorders, schizophrenia, and dementia conducted with each patient by two psychiatrists. (Absolute agreement between the two psychiatrists was necessary for the patient to be included in the protocol.) Any potential

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TABLE 1. Melatonin Levels of Demented, Depressed, Schizophrenic, and Control Subjects Before and After Taking 40 mg of 5-Methoxypsoralen

				Melatonin Level (nmol/liter)					
		Age (years)		Baseline		3 Hours After 5-Methoxypsoralen		Change	
Group	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Healthy elderly subjects (control group 1)	13	73.31	9.66	0.19	0.08	0.42	0.20[a]	0.22	0.18[b]
Demented patients	13	77.92	5.98	0.21	0.10	0.28	0.13[a]	0.06	0.08[b]
Healthy middle-aged adults (control group 2)	13	52.15	12.75	0.16	0.06	0.36	0.15	0.20	0.13
Depressed patients	13	55.46	16.03	0.22	0.10	0.39	0.25	0.17	0.15
Healthy young adults (control group 3)	13	33.46	8.66	0.16	0.08	0.36	0.18	0.21	0.15
Schizophrenic patients	13	35.20	11.05	0.21	0.15	0.48	0.15	0.15	0.08

[a] Significant difference between demented patients and healthy elderly control subjects ($t=2.07$, df=24, $p<0.05$).
[b] Significant difference between demented patients and healthy elderly control subjects ($t=2.82$, df=24, $p<0.01$).

subject with a history of concomitant major medical illness such as hypertension, diabetes, or other endocrinopathy and abnormal physical or laboratory findings was excluded. All the patients were drug free for at least 4 days before the test, except that some were taking nitrazepam, 5 mg, or triazolam, 0.25 mg, at night. All the subjects were informed of the purpose of the study before their written consent was obtained.

A single dose (40 mg) of 5-methoxypsoralen (Psoraderm, Goupil Laboratories, Paris) was administered orally at 8:00 p.m. to each subject. In order to avoid any side effects related to the photosensitizing properties of psoralens (14), the patients and the control subjects were kept in dim light (without ultraviolet light) or in complete darkness for at least 9 hours after administration of the drug (a period corresponding to the normal sleep period). Plasma samples were drawn at 8:00 p.m., before the drug was given, and at 11:00 p.m. through an indwelling catheter inserted in an antecubital vein at least 20 minutes before the first sample was drawn. The samples were immediately centrifuged at 4 °C and frozen at −20 °C until assayed. Plasma levels were estimated by radioimmunoassay after diethyl ether extraction using the Tiefenauer and Andres method (15) (iodine-125, Tecova, Lyon, France). The reliability of the melatonin assay was assessed by studying the cross-reactivities with other indolamines (5-methoxytryptamine, <0.05%; *N*-acetylserotonin, <0.02%; L-tryptophan, <0.01%; serotonin, <0.01%). No cross-reactivity was detected between the melatonin assay and 5-methoxypsoralen at the doses we used. The intra-assay variability was less than 6% at a 0.58-nmol/liter concentration. The sensitivity of the assay was 0.02 nmol/liter. Melatonin levels were averaged and compared within groups by means of paired t tests and between groups by means of unpaired t tests. As age may influence endocrine response, we only compared groups of similar mean age. Change in melatonin level was defined as the difference between the baseline melatonin level and the level after 5-methoxypsoralen was given.

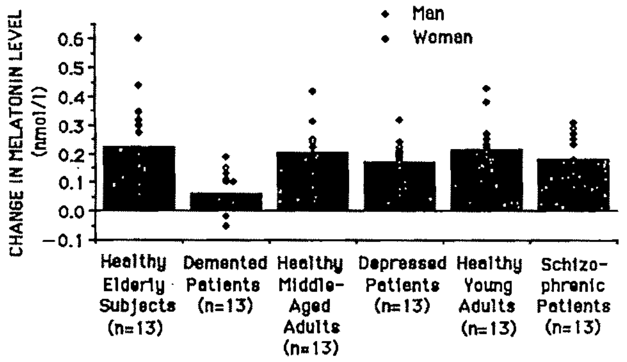
RESULTS

None of the patients reported any side effects after receiving the 5-methoxypsoralen. The data on melatonin levels are shown in table 1. The melatonin level was significantly increased after administration of 5-methoxypsoralen in the three control groups ($t=4.59$, df=12, $p<0.001$; $t=4.18$, df=12, $p<0.001$; $t=3.92$, df=12, $p<0.001$) as well as in the depressed ($t=2.29$, df=12, $p<0.05$) and schizophrenic ($t=8.31$, df=12, $p<0.0001$) patients. However, the increase was not significant in the demented patients ($t=1.88$, df=12, $p>0.05$). The level of melatonin after 5-methoxypsoralen was lower ($t=2.07$, df=24, $p<0.05$) in the demented patients than in the elderly control subjects. In the control subjects, we failed to detect any significant correlation between age and baseline melatonin level ($r=-0.05$, df=12, $p>0.05$), age and melatonin level after the drug was given ($r=-0.08$, df=12, $p>0.05$), or age and change in melatonin level ($r=-0.11$, df=12, $p>0.05$). The mean change in melatonin level was significantly smaller ($t=2.82$, df=24, $p<0.01$) in the demented patients than in the elderly control subjects.

DISCUSSION

The significant increase in plasma melatonin levels observed in five of the six groups after 5-methoxypsoralen administration is entirely consistent with our previous report on healthy young subjects (13). The lack

FIGURE 1. Individual and Mean Changes in Melatonin Levels[a] in Demented, Depressed, Schizophrenic, and Control Subjects After Taking 5-Methoxypsoralen



[a] Change in melatonin level was defined as the difference between the baseline level and the level 3 hours after taking 40 mg of 5-methoxypsoralen.

of correlation between the baseline or postdrug levels of melatonin and age in the control subjects stands in contrast with recent studies showing a decrease in the nocturnal peak of melatonin as a function of age (16–19). However, the mechanisms involved in the nocturnal surge of melatonin and in the pineal response to 5-methoxypsoralen may be different, as suggested by the lack of suppression of melatonin secretion in healthy volunteers treated with 5-methoxypsoralen and exposed to bright light (20).

The relatively large variability of the melatonin response among the subjects within each group (see figure 1) may be related to interindividual variability in the pharmacokinetic characteristics of 5-methoxypsoralen (21). Differences in body measures such as weight and height may also have affected the melatonin response to the drug (22).

We failed to observe a significantly decreased melatonin response to 5-methoxypsoralen in the depressed patients. This finding conflicts with recent reports of impaired nocturnal secretion of melatonin in depression (1–4). The depressed patients' normal melatonin response to 5-methoxypsoralen suggests that the pineal gland's responsiveness to certain stimulating agents may not be impaired in these patients. Moreover, this normal melatonin response of depressed patients to 5-methoxypsoralen may be affected by age, and a similar response might not be observed in elderly depressed patients.

The major finding of this preliminary study was the blunted melatonin response of the pineal gland to 5-methoxypsoralen in the demented patients. Age cannot account for this result, since we compared control and demented groups of similar mean age. The response to 5-methoxypsoralen itself seems to be involved, since the baseline levels of plasma melatonin did not differ significantly. This finding is consistent with preliminary data on demented (Alzheimer type) patients, whose nocturnal surge of melatonin was dramatically reduced compared to that of elderly control subjects (6). This finding may be of great interest, since a decreased melatonin response may reflect a neuropathological abnormality, as suggested by the disturbed function of the pineal gland in familial amyloid neuropathy (23).

However, further investigations of the pineal response to 5-methoxypsoralen in larger samples are needed. Individual evaluations of the intensity of depression or dementia may also be of great interest, in order to assess the possible relationship between the magnitude of the melatonin response to 5-methoxypsoralen and the degree of impairment.

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Differential Effects of Right Unilateral and Bilateral ECT on Heart Rate

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In a series of 11 melancholic patients who received both right unilateral and bilateral ECT during a single course of treatment, mean and minimum postictal heart rates were greater after bilateral ECT. Greater catecholamine release during bilateral ECT is the most likely explanation for these effects. These differences complement other evidence that bilateral ECT has a more pronounced physiological impact than unilateral ECT.

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The elevation in heart rate that accompanies ECT results from the combined effects of the preanesthetic and anesthetic medications and the physiological effects of the induced cerebral seizure discharge (1–4). The effect of the seizure discharge on heart rate is illustrated by the finding that certain measures of the duration of heart rate elevation correlate highly with all other measures of seizure duration (5). Although heart rate can remain higher than preanesthesia baseline levels for up to 1 hour after ECT (3, 4), there is an acceleration of heart rate at the beginning of the seizure and a deceleration of heart rate at the end, both of which occur far too abruptly to be explained by changes in circulating catecholamines, which take 1–2 minutes to drop by 50% (3). Therefore, direct neurogenic adrenergic outflow through paravertebral sympathetic ganglia is probably the dominant autonomic influence on heart rate during the seizure, and circulating catecholamines remaining from ictal release (as well as residual atropinic drug activity) may be the dominant postictal autonomic influence. Because the sympathetic component of these influences, both neurogenic and humoral, is likely to be affected by the field intensity of the ECT electrical stimulus and the intracerebral distribution of the induced seizure discharge, the characteristics of heart rate elevation during ECT can be expected to depend on these same parameters.

Bilateral ECT and right unilateral ECT have differing clinical (6), neuropsychological (7), EEG (8), and neuroendocrine (9–11) effects, with bilateral ECT exerting more pronounced activity in each instance. Greater or more complete intracerebral seizure generalization with bilateral than with right unilateral ECT is suggested by the observations that postictal EEG suppression is greater after bilateral than after right unilateral ECT (12, 13) and that several measures of seizure duration are more highly intercorrelated during bilateral than during unilateral ECT (14). Although the only previous study comparing heart rate response to bilateral and right unilateral ECT found no differences between the two methods in peak postictal heart rates (15), there were different patients in each treatment group and peak heart rate was only measured postictally at 1-minute intervals for 5 minutes. The existence of ECG records obtained for other purposes enabled us to examine heart rate response before, during, and after seizures in patients who had received both bilateral and right unilateral ECT as part of the same course of treatment. On the basis of the considerations we have mentioned, we predicted that elevation of heart rate with bilateral ECT would be greater than that with right unilateral ECT.

METHOD

The general study method has been described in detail elsewhere (5). Briefly, the present study included 11 melancholic patients who received both right unilateral and bilateral ECT administered consecutively during their treatment course according to a research protocol determined before treatment. ECG tracings were available in each instance. Four patients were given right unilateral ECT first, and seven patients were given bilateral ECT first. General anesthesia was given with atropine, methohexital, and succinylcholine. Seizures were induced with a Somatics Thymatron brief-pulse instrument set to deliver a stimulus of 378 millicoulombs (0.9 A, 1.0-msec pulse width at 140 pulses/second for 3 seconds). Each ECG tracing was

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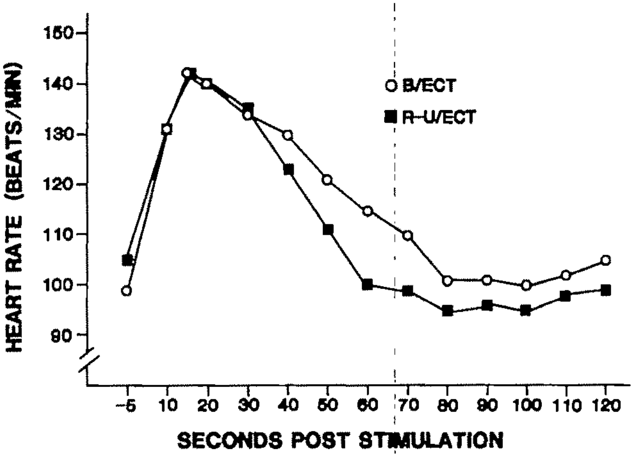
FIGURE 1. Mean Heart Rate Response of 11 Patients After Right Unilateral (R-U) and Bilateral (B) ECT



examined by an investigator blind to treatment electrode placement, and the following measures were obtained: prestimulus (after anesthesia) heart rate, peak heart rate, time elapsed from termination of the ECT stimulus to maximum heart rate; three-beat average heart rate centered at each of 12 10-second intervals following termination of the ECT stimulus, and minimum heart rate during this 120-second period. Seizure duration was estimated separately and also blindly as the time elapsed between termination of the ECT stimulus and cessation of all paroxysmal motor activity in the patients.

RESULTS

There were no differences between the right unilateral and bilateral ECT conditions in motor seizure duration, dose of atropine, or dose of methohexital. With the exception of one patient whose dose of succinylcholine was 10 mg greater with bilateral ECT, doses of succinylcholine were identical under the two conditions.

Figure 1 shows prestimulus heart rate, peak heart rate, and mean heart rate at each 10-second interval for 120 seconds after stimulation. Paired t tests revealed no differences in prestimulus heart rate, peak heart rate, or the time to reach the peak heart rate. However, the minimum heart rate with bilateral ECT (mean±SD=94.5±21.8 bpm) exceeded that with right unilateral ECT (88.4±23.5 bpm) ($t=2.81$, $df=10$, $p<0.01$, one-tailed). A repeated measures analysis of variance was performed on prestimulus heart rate and heart rate at each 10-second interval for 90 seconds (there were 15 missing data points over the last 30 seconds). Main effects were observed for treatment condition (electrode placement) ($F=4.30$, $df=1, 10$, $p<0.05$) and time interval ($F=20.05$, $df=8, 80$, $p<0.0001$). There was no interaction between treatment condition and time interval ($F=1.66$, $df=8, 80$, n.s.).

A post hoc analysis using the Newman-Keuls test revealed that heart rate during bilateral ECT significantly exceeded that during right unilateral ECT 40 seconds after the stimulus, and this difference remained at the $p<0.05$ level or better (two-tailed) for each 10-second interval thereafter, except for 90 seconds, where $p<0.10$.

DISCUSSION

The largest mean differences between the groups occurred from 40 to 120 seconds after the stimulus. This time interval corresponds to the postictal period, since the mean motor seizure duration was about 43 seconds for both groups. The most parsimonious explanation of the greater postictal heart rate with bilateral ECT is that bilateral ECT releases more circulating catecholamines during the seizure than does right unilateral ECT, through neurotransmitter mechanisms in the brainstem (16). This is consistent with the more pronounced action of bilateral than right unilateral ECT on pituitary prolactin release (9–11, 17), also regulated by brainstem neurotransmitter mechanisms, and might result from greater intracerebral generalization of seizures with bilateral ECT or from a larger electrical charge through the brain with bilateral than with unilateral ECT (18). That the ECT electrical stimulus by itself can affect brainstem neurotransmitter release is suggested by Abrams and Swartz's (17) observation of prolactin release following an ECT stimulus in the absence of observable seizure activity; it is also suggested by the demonstration (3) that doubling the intensity of the electrical stimulus during electroconvulsive shock in dogs produced more than a fourfold increase in epinephrine release (although that study did not report seizure duration).

An alternative explanation for these findings is that differences in heart rate response result from differences between right unilateral and bilateral ECT in the laterality of postictal hemispheric activation. Several lines of evidence (19–22) suggest that right hemisphere activity is more closely associated with regulation of heart rate than is left hemisphere activity. Furthermore, animal and human studies have demonstrated that the sympathetic (23, 24) and parasympathetic (25) innervation of the heart is asymmetrical, with right- but not left-side fibers supplying the sinoatrial node. Thus, postictal differences in the laterality of hemispheric activation, if they exist, could accentuate a right-side predominance of sympathetic relative to parasympathetic input to the heart. However, to the extent that humoral sympathetic effects exert a stronger influence postictally than do direct neurogenic effects, this explanation is less likely.

The critical test between the two models requires a comparison of the heart rate effects of right-side and left-side unilateral ECT; such a study is now in progress.

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Imipramine and Alprazolam Treatment of Lactate-Induced Acute Endogenous Distress in Nonhuman Primates

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The authors studied the response of 10 macaque monkeys to administration of sodium lactate, a panicogenic agent used in human panic disorder research, after treatment with the tricyclic antidepressant imipramine, the triazolobenzodiazepine alprazolam, or placebo. Both drugs effectively blocked the lactate-induced acute endogenous distress responses that had been reliably observed in the monkeys before drug treatment. Only alprazolam significantly reduced the occurrence of conditioned situational anxiety responses observed in the home cage. The alprazolam monkeys appeared to be sedated compared to the imipramine and placebo groups, and tremor and temporary exacerbation of anxious behaviors were observed during alprazolam withdrawal.

(Am J Psychiatry 1989; 146:1044–1047)

Panic attacks in human patients are thought to be triggered most commonly by nonspecifiable internal events, whether those events are cognitive ("fear of fear") or physiological (e.g., sudden changes in cardiovascular function) (1). In fact, patients often report that their panic attacks occur spontaneously and are not obviously related to environmental cues or precipitating events (2). The occurrence of panic in the absence of apparent eliciting stimuli distinguishes panic disorder from other anxiety disorders, such as simple phobia, in which the phobic response occurs in reaction to a specifiable feared object.

The clinical distinction between panic disorder and other anxiety diagnoses has resulted in the development of different therapeutic approaches for these two classes of symptoms. Thus, the use of antidepressant medication to block panic attacks is widely documented, whereas anxiolytics most commonly used in the treatment of generalized anxiety have reportedly been relatively ineffective in alleviating panic symptoms (2, 3). However, some of the sequelae of panic attacks, e.g., anticipatory anxiety and agoraphobia, are characterized by symptoms typical of anxiety disorders, which are responsive to standard anxiolytic treatment (4).

The clinical investigation of panic disorder in humans has used an induction model in which the major symptom of the disorder, i.e., panic attacks, can be pharmacologically produced in a large percentage of patients vulnerable to panic (5). The most widely tested model involves the intravenous infusion of sodium lactate, which has been shown to induce the cognitive, emotional, and measurable physiological components of panic attacks in susceptible patients; control solutions generally have failed to elicit panic in patients, and neither lactate nor placebo administration elicits panic in normal subjects (6). Therapeutic interventions that specifically block spontaneous panic attacks, such as tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), have also proved effective in blocking lactate induction of panic in laboratory settings (7, 8).

This experimental human model, based initially on observations that lactate production in panic-prone individuals during exercise (5) often coincided with panic attacks, seems promising as a technique for modeling panic disorder in primate subjects. The range and complexity of the individual and social affective behavior of nonhuman primates can facilitate the establishment of the relevance and generalizability of the symptoms elicited during treatment with lactate, a most important consideration in animal models of human psychopathology.

The study we report is part of a research program on the development of a nonhuman primate model of panic disorder and its clinical application to issues of etiology, mechanisms, and treatment (9). Using the lactate induction of panic model, we have elicited affective distress in primate subjects and, in a preliminary drug study, have blocked that response with the administration of the tricyclic antidepressant imipramine (9).

The specificity of response to a particular class of drugs has obvious importance to the effective treat-

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ment of panic disorder in human patients. In addition, a number of issues related to diagnosis and underlying mechanisms are unresolved in the literature on human research and clinical practice. The current study follows up our initial observations (9) on affective distress elicited by lactate administration to monkey subjects with a controlled comparison of the effects of two drugs used extensively in the treatment of panic disorder, imipramine and alprazolam. Alprazolam is a triazolobenzodiazepine that has become an alternative to tricyclic antidepressants and MAOIs as a panic blocker (10).

METHOD

The subjects were 10 adult male bonnet macaque monkeys (*Macaca radiata*), born and reared in social groups in our primate laboratory. This group was composed of five subjects (out of a screening group of eight males) determined to be highly responsive to lactate in a previous study (9), two additional subjects previously tested in pilot work, and three subjects tested for the first time (the latter five were drawn from a screening group of six males). Seven of these subjects had been exposed to either placebo or imipramine treatment in addition to several previous lactate and dextrose control trials (9). The current study began approximately 1 year after conclusion of previous treatment or testing, and all subjects were randomly assigned to the treatment conditions of the current study. For the duration of the lactate infusion studies, the subjects were housed in individual cages measuring 0.83 m wide, 0.90 m deep, and 2.1 m high. The home cage contained a movable back panel that permitted subjects to be restrained for injections. Each test pen contained three staggered shelves, overhead fluorescent lighting, and an 8-sq. ft. one-way mirror in the front door. Animals received water as needed and were fed once a day. Detailed procedures for administration of lactate and dextrose solutions, observational records, and behavioral measures have been described elsewhere (9). While being restrained in their home cages, the subjects received subcutaneous injections of 0.5 M racemic sodium lactate, 10 mg/kg of body weight, or 5% dextrose in sterile H_2O. As described in our previous work (9), this mode of administration allows a wide range of behaviors in the freely moving animals and is well tolerated by our subjects. After 10 minutes, they were released into the test pen for a 60-minute behavioral observation trial. After their test trials, the subjects were returned to their home pens.

Before drug and placebo administration, all subjects received two lactate and two dextrose control trials over a period of 4 weeks. Each 60-minute behavioral observation trial was videotaped through the one-way mirror in the front door of the test pen. These tapes were analyzed by a rater blind to treatment condition who assigned an acute endogenous distress score that represented the occurrence of any one of 32 behaviors, which, on the basis of 25 years of behavioral assessment of macaque monkeys, have been judged to be symptomatic of high levels of distress and arousal (11). Eight weeks after the initial lactate and dextrose trials, all subjects, who had been shown to be lactate sensitive, were started on drug regimens. Drugs and placebo were delivered to subjects orally in pieces of banana in the home cage. Three subjects received imipramine hydrochloride tablets, beginning at a dose of 1.5 mg/kg of body weight per day, which was increased by increments of 0.5 mg/kg weekly over a period of 4 weeks until a daily dose of 3.5 mg/kg of body weight (a dose usually therapeutic for humans) was reached. Three subjects received alprazolam tablets, beginning at a dose of 0.02 mg/kg daily (the equivalent of 1.5 mg/day in humans), which was increased by increments of 0.01 mg/week over 4 weeks until a daily dose of 0.053 mg/kg (the equivalent of the usually therapeutic human dose of 4 mg/day) was reached. Placebo pills were administered to four subjects over the same time period.

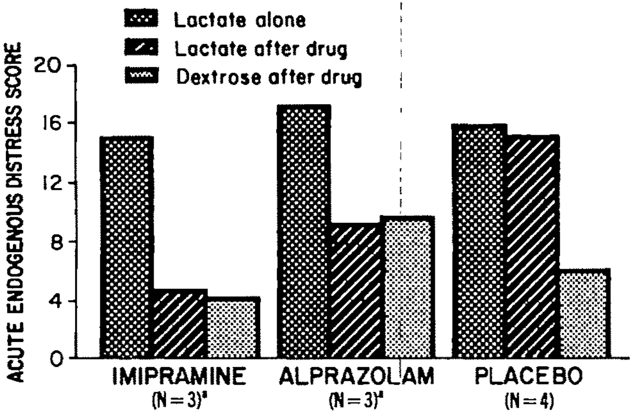
During weeks 5 and 6 of drug administration, the subjects were given two lactate and two dextrose trials, counterbalanced for order of lactate and dextrose trials, and acute endogenous distress scores were again assigned from videotapes of each behavior observation trial by a rater blind to drug condition.

During the predrug lactate and dextrose testing, the subjects began to display behaviors in their home cages (in which they were restrained for injections) that seemed indicative of emotional disturbance. These "cage behaviors," including locomotor and affective arousal (e.g., pacing, threat gestures and vocalizations, fear grimaces, and huddling in the corner), were observed to escalate in frequency and intensity when the experimenter approached to administer pieces of food that contained the experimental drugs or placebo. As a consequence, these behaviors were rated daily during the 5–6-week drug trial on a scale of 0–3 for intensity and frequency when the experimenter approached the subject's cage. These data were analyzed for the two drug groups and the placebo group during weeks 5 and 6 of drug treatment.

RESULTS

Before drug treatment, the subjects' acute endogenous distress scores were higher after lactate than after dextrose injections. The mean±SD lactate-induced acute endogenous distress score per 60-minute trial for all subjects was 15.6±3.7, and the mean±SD score for the dextrose control trials was 6.24±3.0. The fact that all subjects had higher acute endogenous distress scale scores after lactate infusion than after dextrose infusion indicates that they were responsive to lactate. The observers' overall impression of the subjects' response to lactate, in addition to the quantitative rating scale measures, was of increased agitation, fearfulness, and irritability. These behaviors were exhibited by the sub-

FIGURE 1. Mean Acute Endogenous Distress Scores of 10 Macaque Monkeys in Response to Predrug Lactate Injection and to Postdrug Lactate and Dextrose Injections



[a] Response to lactate after drug treatment significantly lower than response of same group to lactate alone (imipramine: $t=4.99$, $df=2$, $p<0.03$; alprazolam: $t=4.32$, $df=2$, $p<0.03$).

jects while they were alone in the test pen and without exposure to any eliciting stimulus other than the sodium lactate. Behavior during dextrose trials did not appear different from baseline observations before dextrose injection.

The acute endogenous distress scores obtained after the two lactate and two dextrose trials during weeks 5 and 6 of drug treatment indicated that neither drug group responded differently to lactate than to dextrose (figure 1). Treatment with either the tricyclic antidepressant imipramine or the triazolobenzodiazepine alprazolam blocked the induction of acute endogenous distress during the lactate trials. The acute endogenous distress scores of the placebo group were not significantly different after placebo than before placebo.

We also compared mean rating scores for home cage anxiety for the first week (drug week 1) to scores for the week during which the maximum therapeutic dose was reached (drug week 5 or 6). The alprazolam subjects appeared generally sedated during drug treatment, but the monkeys receiving imipramine did not appear to show a change in their level of alertness and responsivity to stimuli. Although imipramine successfully blocked lactate induction of acute endogenous distress, it failed to produce any reduction in the levels of cage behavior; however, alprazolam treatment resulted in significantly lower levels of cage distress behavior when the maximum dose had been reached ($t=2.95$, $df=2$, $p<0.05$). The placebo group also failed to show a reduction in cage distress behaviors. Alprazolam, therefore, appeared to block lactate induction of acute endogenous distress and to alleviate the symptoms of disturbance observed in the home cages in the presence of the experimenter.

The alprazolam subjects experienced some difficulty during the withdrawal period. As the dose was gradually decreased over 3 weeks, there was some apparent rebound anxiety during home cage observations, evident in transient increases in fear and irritability, as well as tremor (observed in two subjects). All subjects were successfully withdrawn from alprazolam, however, and did not appear to suffer any lasting ill effects.

DISCUSSION

In this study we compared the effectiveness of imipramine and alprazolam as blockers of lactate-induced acute endogenous distress in our nonhuman primate subjects. As in our previous work (9), primates responded to subcutaneous injections of sodium lactate, but not to dextrose injections, with affective distress. Pharmacological treatment with agents that have been shown in the human literature to be panic blockers effectively attenuated lactate-induced acute endogenous distress in our primate model.

A serendipitous finding was that the monkeys, over the course of the lactate infusion study and before drug administration, began to exhibit behavioral disturbance, manifested as heightened levels of pacing, vocalization, fear grimaces, and huddling, during exposure to previously neutral stimuli. No such agitation had been observed before the study began, either as a result of routine handling or at the approach of the experimenter. However, after repeated restraint and injection of both sodium lactate and dextrose in the home cage, the subjects began to exhibit discrete episodes of disturbance when exposed to either of these stimuli, behavior that suggests the development of a situational fear response similar to anticipatory anxiety in human patients.

After pharmacological treatment, those animals treated with alprazolam showed a decrease in this form of conditioned situational anxiety. The subjects treated with imipramine or placebo continued to exhibit behavioral disturbance in the home cage, although the acute endogenous distress response to lactate infusion per se was blocked in both treatment groups. Klein (2) has hypothesized that in humans different pharmacological agents affect panic and anticipatory anxiety differently. Our data suggest some interesting parallels with this clinical observation. We also observed effects of alprazolam similar to those reported by Fyer et al. (12) in humans. Our animals appeared to be sedated after alprazolam, and even gradual withdrawal, following clinical protocols, led to some degree of rebound anxiety and tremors.

We are currently developing this primate model of lactate-induced acute endogenous distress using a number of anxiogenic and panicogenic substances in combination with different therapeutic agents. A nonhuman primate model can make possible a variety of studies that would prove difficult or impossible with human subjects. For example, lactate dose-response studies can help establish whether lactate induction of panic demonstrates an absolute biological susceptibility or differential threshold effects in responders and nonresponders (13). The measurement of CSF levels of such substances as catecholamines and their metabolites, as well as central administration of lactate, can be used in animal subjects to investigate central and peripheral mechanisms of panic disorder. Finally, the prospective manipulation of social and environmental variables during development will make it possible to test different theories of the etiology and pathogenesis of anxiety and panic.

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Head Injury and Marital Aggression

Alan Rosenbaum, Ph.D., and Steven K. Hoge, M.D.

Of 31 consecutive male patients referred for evaluation of marital violence, 19 (61.3%) had histories of severe head injury. Although the relationship between child abuse and head injury did not reach an acceptable level of significance, it did indicate a trend toward a positive relationship. Alcohol abuse, reported by 48.4% of the sample, was significantly associated with head injury. Confirmation of biological etiologies in marital aggression would have implications for prevention and treatment.

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Recent estimates indicate that almost two million American women are abused by their male partners each year; 30% of the women who are murdered are killed by their partners, and more than 30% of women will be victims of their partners' aggression during the course of their relationships (1). Further, aggression between partners often begins before marriage. The results from a recent prospective investigation of beginning marriages indicate that premarital aggression occurred in about half of the 396 couples (2). Marital violence exacts significant social costs, which include a high divorce rate; strain on law enforcement, the legal system, jails, medical care, shelters, and welfare resources; and time lost from work. It is a major contributor to psychiatric, emotional, and stress-related medical problems for all members of affected families. The magnitude and seriousness of this problem recently prompted the Surgeon General of the United States to designate domestic violence an important public health priority.

Although marital violence has long been a victim of professional and academic inattention, in the last decade it has begun to attract the interest of researchers, clinicians, and academicians from a variety of disciplines, and our knowledge of this phenomenon has consequently increased. However, efforts to understand the etiology of marital violence have focused on psychosocial agents; the potential contributions of physiological factors have not been explored empirically. Workers in the field have speculated on the role of biological factors in marital violence. In 1977, Roy included an article on episodic dyscontrol syndrome (recurrent attacks of rage and violence) in her anthology *Battered Women* because, she wrote, "Physical disorders of the brain are sometimes responsible for wife battery, though, as yet, there is no data on what proportion of wifebatterers [sic] are so affected" (3). Similarly, in that report on episodic dyscontrol syndrome, Elliott (4) stated, "It is an important cause of wife and child battery." Over 10 years later there are still no data on what proportion of wife batterers have such physical brain disorders. Hotaling and Sugarman (5) reviewed 97 potential risk markers of husband-to-wife violence distilled from over 400 empirical reports, but biological factors were notably absent.

Links between biological factors and generalized aggression have been studied more extensively. A number of researchers and clinicians have suggested a relationship between neurological injury and aggression. Lewis et al. (6) reported histories of severe head injuries in all of the 15 violent criminals they studied. This was confirmed by their more recent study (7) of 14 juvenile murderers. All 14 were reported to have experienced severe head injuries; 12 had been physically abused as children. Elliott (8) observed that in 102 of 286 cases of episodic dyscontrol syndrome, the condition developed after a specific brain insult. In a study by McKinlay et al. (9), approximately 70% of patients who had received traumatic brain injuries were shown to have aggression and irritability that was significantly distressing to themselves and their families. Detre et al. (10) reviewed experimental animal studies and clinical reports involving humans and concluded that there is convincing proof of an association between neurological impairment and violent behavior. They went on to state that violent behavior is one sequela of "head traumas severe enough to cause loss of consciousness." Lishman (11) suggested that aggressive behavior results from reduced control consequent to damage to frontal lobe structures.

In addition to the association between head injury and other forms of aggression, the potential significance of head injury in the etiology of marital aggression is bolstered by the striking similarities between the behavior of patients with closed head injuries and wife batterers. Wood described the aggressive behavior typ-

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ically displayed by patients with closed head injuries, which is virtually indistinguishable from that of a wife batterer. Such patients, Wood (12) wrote,

> frequently show a great deal of remorse for an episode of aggressive or destructive behavior over which they appear to have no control. . . . Typically, [he] is subject, under minor provocation, to violent behavior quite out of proportion to the eliciting event. Sometimes such aggression is an exaggeration of . . . personality traits which have become less controlled and more susceptible to the effects of stress, alcohol and frustration. . . . In such cases, aggression is not usually extreme but is a more enduring feature of short temper, noncooperation, abusive language and generally threatening or difficult behavior.

In sum, there is good reason to suspect that biological factors play a role in the etiology of marital violence in a subsample of wife batterers. Despite suggestions to that effect dating back 10 years or more, empirical evaluations of the question are lacking. In this paper we report the results of an exploratory study of the frequency of one factor associated with generalized aggression—previous head injury—in a sample of 31 wife batterers.

METHOD

The Men's Educational Workshop at the University of Massachusetts Medical Center provides outpatient evaluations and treatment for patients with problems of aggression in marital or dating relationships. Patients are self- or court-referred from throughout central Massachusetts and from neighboring states. The subjects consisted of 31 consecutively referred men who were interviewed by one of us (A.R.) over a 1-year period. The initial evaluation included a medical history, which consisted of a series of open-ended questions designed to elicit reports of significant illnesses and accidents during childhood and adulthood. Any report of an accident or illness with potential CNS sequelae was followed up with questions assessing whether medical attention was required, whether a diagnosis having CNS significance was assigned (e.g., concussion), whether there had been a loss of consciousness, and if so, its duration. Subjects who did not spontaneously report head trauma were asked specifically about its occurrence and about the occurrence of events with a high likelihood of causing head trauma (e.g., motor vehicle accidents, fights, playground accidents). A subject was considered to have had a significant head injury if he reported a head injury that was diagnosed as a concussion by a physician or if he experienced a loss of consciousness as a result of the injury. All but two of the men who met either criterion reported some period of unconsciousness. The subjects were also queried regarding family history, including the occurrence of childhood maltreatment; history of aggression toward their female partners, children, and others; alcohol and drug use; and demographic information.

All but two of the subjects were white. Their mean ±SD age was 29.7±6.3 years.

RESULTS

Nineteen subjects (61.3%) had positive histories of head injury diagnosed as concussion or causing loss of consciousness (see table 1). The mean±SD age at the time of injury was 16.1±5.2 years. Motor vehicle accidents were the most frequently reported causes of the injuries. In 17 of the 19 cases (89.5%) the subject reported loss of consciousness ranging from several minutes to several months. All of the subjects, by design, physically abused their female partners. Six of the 19 subjects with histories of head injury also reported aggression toward others; this was true for only one of the subjects without head injuries; this subject abused other family members. The between-groups difference was not statistically significant, possibly owing to the small sample size.

A history of having been abused as a child was reported by nine (47.4%) of the 19 men with histories of head injury but by only one (9.1%) of the 11 men without head injury on whom data were available; this difference was statistically significant ($p=0.037$, Fisher's exact test). Significantly more of the subjects with head injuries reported alcohol abuse (68.4% versus 16.7%; $p=0.006$, Fisher's exact test).

DISCUSSION

In the absence of a control group, the magnitude of the frequency of head injury found in this investigation can be appreciated only by comparison with the base rate in the general population. While no prevalence estimates are available, the yearly incidence of head injury is approximately 0.2% (13). A rough estimate of prevalence can be made by multiplying this figure by the mean age of our sample, resulting in a rate of 5.9%. Thus, the rate of head injury found in our sample (61.3%) far exceeds that found in the population at large. The strong association between head injury and alcohol abuse raises interesting questions about the relationship between head injury and aggression. One possibility is that alcohol abuse represents a third variable, which promotes both head injury and aggressiveness. Many of the reported head injuries were caused by motor vehicle accidents, and alcohol use is associated with vehicular mishaps. However, a review of the data on age at injury in table 1 suggests that many of the head injuries occurred before the subjects would have been likely to have been abusing alcohol. Alternatively, according to Elliott (4, 8), oversensitivity to alcohol is associated with episodic dyscontrol syndrome, which itself has been attributed to head trauma. A third possibility is that the combination of alcohol and head injury renders an individual particularly vulnerable to aggressive behavior. If alcohol and

TABLE 1. Characteristics of 19 Men Evaluated for Marital Aggression Who Had Histories of Head Injury

Subject	Age (years)	Age at Injury (years)	Nature of Injury	Duration of Unconsciousness	Target of Aggression	Abused as Child	Alcohol Abuse
1	29	13	Open head injury	Weeks	Generalized	Yes	Yes
2	29	17	Open head injury	Days	Generalized	Yes	Yes
3	30	28	Concussion	—	Wife	—	Yes
4	22	19	Concussion (automobile accident)	Unknown	Wife	—	Yes
5	26	19	Concussion (automobile accident)	Minutes	Wife	—	Yes
6	33	—	Concussion	Minutes	Wife	Yes	Yes
7	37	11	Concussion (automobile accident)	Months	Family	—	Yes
8	35	17	Concussion	Minutes	Wife	Yes	—
9	27	22	Concussion (automobile accident)	Minutes	Wife	—	Yes
10	30	18	Concussion	Minutes	Generalized	—	—
11	28	12	Concussion	Minutes	Wife	—	—
12	33	11	Concussion	Hours	Wife	—	Yes
13	23	11	Concussion	Unknown	Wife	Yes	—
14	30	23	Concussion	Unknown	Wife	—	—
15	38	10	Concussion (automobile accident)	Days	Generalized	—	—
16	42	17	Multiple concussions	—	Wife	Yes	Yes
17	29	20	Multiple concussions	Minutes	Wife	Yes	Yes
18	21	10	Concussion	Minutes	Wife	Yes	Yes
19	25	11	Concussion	Minutes	Generalized	Yes	Yes

head injury each promote aggressive behavior, the combination might have an additive, or even a synergistic, effect.

The finding of an association between head injury and a history of child abuse in this investigation is similar to that previously reported by Lewis et al. (7). Further examination of the complex relationships among a history of child abuse, alcohol use, head injury, and marital aggression is clearly warranted.

The implications of our findings will be far-reaching if confirmed by further studies. To date, research in marital violence has been constrained by strictly psychosocial conceptualizations of abuse. Consideration of biological etiologies will suggest new approaches to the understanding, assessment, and treatment of these often refractory patients. Efforts to understand the mechanisms by which head injury promotes aggression may lead to the development of new and effective treatment approaches. M.R. Lansky, for example, has been quoted (14) as suggesting that closed-head injuries promote self-esteem deficits which precipitate shame-induced rage and aggression, suggesting new foci for psychotherapy. Others (11) see a more direct, organic relationship with implications for pharmacological treatment. Additional benefits of discovering biological etiologies include the potential for indentifying groups at high risk for development of marital aggression (e.g., patients with histories of head trauma), who could be targeted for early intervention and prevention.

Our results are consonant with the work of researchers who have suggested the importance of head injury and other biological factors in the production of generalized aggressive behavior. In fact, the patients in the studies of violent behavior in general may not have been completely distinct from individuals who are violent toward their partners. In our sample of men who physically abused their partners, seven patients reported victimizing individuals other than their wives; in four instances the victims included people other than family members. It is likely that such behavior is underreported, and the overlap of these populations may be even more substantial. Furthermore, spouse abuse may be underreported and unrecognized in patients seen because of more generalized violence.

This investigation had several methodological shortcomings, inherent in an uncontrolled, nonblind study, which suggest caution in interpretation of the findings. Without appropriate control groups we are unable to exclude other explanations for the high rate of head injury found in our sample. It is possible, for example, that head injury contributes to marital dissatisfaction among men—some portion of whom will be violent—but not specifically to marital violence. It is also plausible that violence-prone individuals may be more likely than the general population to engage in dangerous activities which would increase the chances of bodily injury. The fact that the data were collected through interviews by the investigator, who was not blind to either the behavior of the subjects or the theory being tested, raises the possibility of experimenter bias in the ascertainment of CNS insult. Replication of these findings based on standardized measures of alcohol use and child abuse and a design that minimizes the possibility of experimenter bias would increase our confidence in these results.

Finally, the fact that the Men's Educational Workshop, the source of our sample, is a hospital-based program increases the potential for a Berksonian bias. Berksonian bias refers to an unknown selection bias operating to produce the illusion of a relationship. In the present study, for example, it is possible that men treated at the medical center for head trauma were more likely to be referred to the workshop than to an unaffiliated program when marital problems arose. This would result in an artificially inflated number of patients reporting both marital violence and a history of head trauma. The likelihood that a Berksonian bias is operating in our sample is diminished by the fact that there are no alternative programs for batterers within a 30-mile radius. In addition, more than half of our sample suffered their head traumas during childhood and were treated elsewhere.

The results of this preliminary investigation should encourage further empirical examination of the role of physiological factors in the etiology of aggression, marital and otherwise.

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The Normalcy of Self-Proclaimed "Normal Volunteers"

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Volunteers who claimed they were "healthy and normal" and did not reveal any physical or mental abnormality or medication use during brief structured interviews underwent detailed structured interviews with the Schedule for Affective Disorders and Schizophrenia. Diagnoses were based on the Research Diagnostic Criteria (RDC), and family history was determined with the Family History RDC. Of the 121 volunteers, 16.5% met criteria for diagnoses of current mental disorders. Of the 104 without current DSM-III *axis I diagnoses, 35.6% had past histories and 39.4% had family histories of mental illness. These results emphasize the need for thorough assessment of "normal volunteers."*

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In most research projects focused on possible clinical or biological abnormalities, it is considered necessary to compare the index group of patients to control subjects with other diagnoses or to "normal subjects." The philosophical question of what constitutes normalcy will always be with us (1); nevertheless, there is a need for some consensus regarding use of the term "normal, healthy volunteers."

For a definition of biological normalcy, the distinction is reasonably clear-cut: a subject who has no evidence of physical disorder and whose results on routine blood, urine, and other tests are "within normal limits" is considered normal. These limits have been statistically derived from studies of large populations. Nonetheless, even in this relatively unambiguous area, controversies arise. There are questions about whether established limits are too narrow (2), whether standardization populations are comparable to a hospitalized population (3), and whether certain demographic characteristics influence mean values (4). With regard to mental disorders, the definition of "within normal limits" or "normal" is complicated by the fact that diagnosis is still descriptive and subjective and may be influenced by the values, ideas, and theoretical background of the diagnostician. Usually the task of identifying "normal subjects" is accomplished through compromise: definition is by exclusion, and "not mentally ill" is accepted as meaning "normal." Even with careful attention to diagnostic detail, the exclusion of several questions in a comprehensive interview can make the difference between meeting the criteria for a diagnosis of a disorder and not meeting them (5).

In the present report we describe our findings from two concurrent studies of variability in mood, behavior, and biological measures. The issues we addressed were 1) the biological and mental pathology found in the volunteer subjects, 2) the lifetime histories and family histories of psychiatric disturbance in those volunteers who were not currently mentally ill, and 3) the need for a structured, in-depth interview for the identification of "normal subjects."

METHOD

The subjects responded to newspaper advertisements and posted notices. They were recruited for two concurrent studies. The first group were young women (aged 20–45 years) who responded to advertisements for "normal women with regular menstrual cycles for participation in studies of the menstrual cycle." Additional young women, postmenopausal women, and men of various ages responded to advertisements for "normal, healthy volunteers for biological studies." These subjects were to serve as control subjects for a study of the hypothalamic-pituitary-adrenal axis in patients with affective symptoms. Advertisements were run in local newspapers covering a working-class borough of New York City (the Bronx) and an upper- and middle-class suburb nearby (Westchester County). Posted notices were placed in and around the medical center and the medical school.

Screening for the premenstrual changes study was

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accomplished in three stages: structured telephone screening, self-ratings and physical and laboratory tests, and structured diagnostic interviews. The telephone screening included 1) questions aimed at detecting use of medications, including psychoactive medication, hormones, and birth control pills, 2) brief medical history of recent pregnancy, miscarriage, abortion, or physical problems (recent physical trauma, surgery, chronic illness), and 3) questions to detect recent or past diagnosed psychiatric disorders ("Were you ever . . . " or "Are you currently diagnosed as having [list of psychiatric disorders])?" and questions on selected symptoms or significant psychopathology according to a checklist aimed mostly at affective and schizophrenic disorders. The telephone contact lasted about 10–20 minutes. Women who met the initial criteria and who were interested in participation were sent three self-rating scales: the Premenstrual Assessment Form (6), a menstrual history form, and the Daily Rating Form (7). The Daily Rating Form ratings were used to evaluate changes in mood and behavior across a 6-week period and to detect evidence of chronic problems throughout the menstrual cycle. Women who met the criteria for one of five subgroups of premenstrual changes (including "no premenstrual changes") and whose reported changes were confirmed by the daily ratings were then physically examined. Blood was drawn for determination of liver and renal function, thyroid profile, blood chemistry, and levels of electrolytes, proteins, and glucose. Routine urine analysis was performed. If the physical and laboratory test results were within normal limits, the subject was asked to participate in the diagnostic interview.

Screening for the affective disorders study was accomplished in two stages. It was virtually identical to that for the premenstrual changes study, with the exclusion of the three self-rating scales pertaining to the menstrual cycle.

The initial screening steps of brief telephone interviews and physical tests reduced the pool of volunteers to 121 subjects, who were each evaluated with a detailed structured interview. They included 53 women of reproductive age (18–48 years), 31 postmenopausal women (aged 45–69), 26 younger men (aged 20–49), and 11 older men (aged 50–76).

The diagnostic interviews were performed by raters (psychologists) who were trained by one of us (J.E.) and for over 6 weeks performed and/or inspected diagnostic interviews with senior experienced raters. The interviews were given with the Schedule for Affective Disorders and Schizophrenia (SADS) (8), and diagnoses were made according to the Research Diagnostic Criteria (RDC) (9). The subjects were also asked about first-degree relatives, who were diagnosed according to the guidelines of the Family History Research Diagnostic Criteria (FH-RDC) (10). Before final diagnosis, each SADS booklet and diagnosis was checked by a psychologist who did not conduct the interview, and they were edited for completeness and consistency by an independent editor.

TABLE 1. Diagnoses and Family Histories of 20 "Normal Volunteers" Given SADS Interviews Who Met the RDC for Current Mental Disorders

	Subjects With Diagnoses		Families With Current or Past Diagnoses
RDC Diagnosis	Current	Past	
Major depressive disorder	3	10	3
Minor depressive disorder	2	1	2
Intermittent depressive disorder	3	0	0
Recurrent unipolar depression[a]	0	4	0
Bipolar II disorder[a]	0	2	0
Other affective disorder	1	2	2
Generalized anxiety disorder	2	2	0
Alcoholism	2	4	8
Drug use disorder	0	2	4
Organic brain syndrome	1	0	0
Phobic disorder	1	0	0
Personality disorder	6	0	0
Bulimia	3	0	0
Schizophrenia	1	0	0
Other psychiatric disorders[b]			
With dysphoria	0	0	5
Without dysphoria	0	0	5
Total			
Diagnoses	25	27	29
Subjects	20	11	8

[a] Because recurrent unipolar depression and bipolar II disorder are illness patterns rather than actual epsiodes, these diagnoses are "lifetime diagnoses." They refer to both current and past episodes.

[b] RDC definition.

RESULTS

Of the 121 subjects who presented themselves as normal, passed the telephone screening, and were judged eligible for SADS interviews, 20 (16.5%) were found to have current psychopathology diagnosable with the RDC (and *DSM-III-R*). Their diagnoses are presented in table 1. These 20 comprised 10 of the 53 younger women (18.9%), six of the 31 postmenopausal women (19.4%), and four of the 26 younger men (15.4%). All the older men who passed the initial screening also passed the SADS interview. Of the 20 currently mentally ill subjects, past histories of diagnosable mental illness were found in 11 (55.0%) (seven younger women, three postmenopausal women, and one young man). Eight (40.0%) of these 20 subjects (six younger and two older women) had first-degree relatives who met criteria for mental disorders. Because any one person may receive multiple diagnoses in the present or past, the total number of diagnoses exceeds the total number of subjects in each column in table 1.

Of the 104 subjects without current *DSM-III* axis I diagnoses (including three with personality disorders), 37 (35.6%) had histories of prior episodes of mental disorder (major depressive disorder, N=19; minor depressive disorder, N=15; generalized anxiety disorder, N=3; alcoholism, N=4; other psychiatric disorders with dysphoria, N=1) (some subjects had more than one diagnosis). They included 25 (56.8%) of the younger women, seven (28.0%) of the postmenopausal women, and five (20.8%) of the younger men.

Information gathered from the subjects without current *DSM-III* axis I diagnoses indicated that 41 (39.4%) had first-degree relatives with current or past mental disorders according to the FH-RDC (major depressive disorder, N=17; minor depressive disorder, N=12; recurrent unipolar disorder, N=8; other affective disorders, N=3; generalized anxiety disorder, N=1; alcoholism, N=12; drug use disorder, N=5; other psychiatric disorders with dysphoria, N=8; other psychiatric disorders without dysphoria, N=8; schizophrenia or other psychosis, N=7). Some subjects had more than one diagnosed relative in their families. The subjects without current diagnoses who had positive family histories included 16 (36.4%) of the younger women, 17 (68.0%) of the postmenopausal women, seven (29.2%) of the younger men, one older man. To test whether the prevalence of positive family history in the subjects who were not currently mentally ill was raised by the inclusion of subjects with past diagnoses, the family history data were reanalyzed to compare only those subjects who had never been mentally ill (N=67) with those who were not currently mentally ill but had past histories of mental disorders (N=37). The two groups did not significantly differ from each other (χ^2=0.93, df=1).

The 20 subjects with current RDC diagnoses were compared with the 104 who did not have current *DSM-III* axis I diagnoses. The prevalence of past history of mental disorder was significantly higher in the group with current mental disorder (55.0%) than in the subjects without current diagnoses (35.6%) (χ^2=4.75, df=1, $p<0.05$); comparison of family histories yielded nonsignificant results (χ^2=0.005, df=1).

DISCUSSION

The main finding of this study was that one-sixth of subjects who presented themselves as normal, healthy volunteers and who passed initial screening actually had current mental disorders diagnosable through SADS interviews. On the basis of this finding, a case can be made for in-depth diagnostic assessments even when volunteers present themselves as healthy and normal or are staff members who are professionally known to the investigators. Additionally, we found that over one-third (35.6%) of the volunteers with no current psychopathology reported diagnosable past mental disorders and 39.4% had first-degree relatives with past or current diagnosable mental illness. Past history and family history were more prevalent in female subjects.

Psychopathology Among Self-Proclaimed "Normal Volunteers"

While we feel that the extent of psychopathology (16.5%) found in our group of volunteers warrants in-depth screening, it was considerably lower than that reported in early studies of "normal volunteers." In three studies of hallucinogenic drugs (5, 11, 12), 38%–41% of the young "normal volunteers" were reported to have diagnosable psychopathology as determined through psychiatric interviews. In a study of older volunteers (13), aged 65–92 years, 65% of the subjects had "diagnosable psychopathology." The method of diagnostic evaluations and criteria applied were not described or discussed. These studies were separated from the current project by 25–30 years; it can be assumed that diagnostic procedures so separated in time are different. It is also possible that some of the earlier diagnoses reflected symptomatic conditions which were not sufficiently severe or numerous to meet typological criteria for actual syndromes. The diagnoses in the current study were confined to symptoms that cluster temporally and constitute a syndrome. Furthermore, in studies of hallucinogenic drugs, subjects' motivation cannot be overlooked. The researchers in those studies may have studied a group with more psychopathology than the subjects in our study, since some reports (11, 14) suggest that subjects motivated by thrill seeking, release from inhibitions, self-discovery, or treatment seeking tend to show a higher prevalence of psychopathology than those who are motivated by financial gain or scientific curiosity.

The high percentage of volunteers in this sample who had current or past diagnoses of affective disorders may have been related to the setting, the purposes of the two studies for which they were recruited, and the volunteers' motivation. This might especially have been the case with the women who volunteered for the study of menstrual changes (32 of the 53 younger women recruited); six met criteria for a current disorder. Many of these women had premenstrual mood changes, and their prevalences of lifetime history and family history of affective disorder were shown to be high (15, 16). When they asked, the other volunteers were told that they were being recruited as control subjects for studies of affective disorders. This purpose is different from the one explained to volunteers for a study of pain (17), who were reported to be "more intelligent, realistic, happy, energetic and optimistic" than a matched group of control subjects.

Thirty-six percent of our subjects without current *DSM-III* axis I diagnoses met criteria for past mental disorders. In studies in which lifetime diagnoses may be hypothesized to be associated with interepisode symptoms or trait-linked biological markers, investigators should be informed on such prior episodes. Such information is needed in making a reasoned decision about a subject's inclusion in a particular study.

Physiological differences have been found between "normal subjects" with and without family histories of mental disorder (18–20). It therefore seems appropriate to note whether there is a family history of psychopathology when using normal subjects for biological studies. In our sample, we found that 39.4% of those without current diagnoses had positive family histories of mental disorder—mostly affective disorders, alcoholism and drug abuse, and psychoses. The prevalence of family history in this group of volunteers, especially a family history of severe disorders, was higher than the prevalence of mental disorders in samples of subjects in the general population (21), who were randomly approached and did not actively volunteer. An association between family history of mental illness and motivation for volunteering for studies of these disorders is feasible. Presently it is unclear whether there is a difference in prevalence of family history between "normal subjects" who actively volunteer and those who are recruited by being individually approached.

Can Generalization From "Normal Volunteers" Be Made?

Normalcy can be defined according to a myriad of criteria, ranging from a statistical majority to a culturally based optimum. Even such potentially quantifiable variables as laboratory chemistry values are subject to debate over limits of normal values (22). When attempts at definition of mental and emotional normalcy are made, the issues become more complex. Schwab (1) commented that while mental health and illness exist on a continuum, a cutoff point must be chosen. He went on to say that the placement of that cutoff point is to some extent influenced by the society and the historical era in which we live. Given the current widespread use of the consensually validated criteria of the RDC and *DSM-III-R*, they seem to be a reasonable guide in choosing a cutoff point between illness and normalcy, although it is plausible that this conceptualization will change in the future.

Once we have excluded from biological studies volunteers with current mental disorders, the next question is whether our remaining "normal subjects" are representative of the general population. In our study, 35.6% of the supposedly normal subjects—those currently not mentally ill—had past psychiatric histories. This agrees with the 28%–38% point prevalence of lifetime diagnoses (including current episodes) found in a large population study (23). That volunteer subjects differ from those who do not volunteer in prevalence of psychopathology has been documented (5, 11–13). The active volunteers in our study also had a high prevalence of family history of mental disorders. All these considerations suggest that caution is needed in the generalization of findings on solicited "normal volunteers" to the population at large. Although the general population consists of a continuum from "totally healthy" to "very sick," active volunteers for a particular study represent only a narrow range of this continuum in the same way that a particular patient group represents another narrow range.

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Association of Left-Handedness With Ventricle Size and Neuropsychological Performance in Schizophrenia

Joanna Katsanis, M.A., and William G. Iacono, Ph.D.

Left-handed schizophrenic patients showed lateral ventricular enlargement and generally poorer performance on intelligence and neuropsychological tests compared with right-handed schizophrenic patients. These results suggest that left-handed schizophrenic patients have more cerebral dysfunction than right-handed schizophrenic patients.

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A number of reports (1–3) have found from 17% to 31% of schizophrenic samples to be nondextral, rates that are well above the 10% proportion usually found in the normal population (4). Such findings raise intriguing questions about the significance of having schizophrenia and being left-handed, an association that has received little attention in the literature. Research published to date has shown that left-handed individuals with schizophrenia have poorer premorbid social competence (2), impaired language functioning (1), ventricular dilation (5), an earlier age of onset (3), and more negative symptoms (6) when compared to right-handed patients. Taken together, these results suggest that left-handed patients with schizophrenia have a severe form of the disorder that might be associated with brain dysfunction. To further evaluate this possibility, the present study was undertaken to determine if left-handed schizophrenic patients showed signs of neurological and cognitive deficit compared to right-handed patients. We hypothesized that left-handed patients would show lateral ventricular enlargement and perform worse than right-handed patients on tests of intelligence and neuropsychological function.

METHOD

Sixty-three schizophrenic patients (56 men, seven women), ranging in age from 17 to 38 years (mean±SD=28.32±4.46), were recruited from an extended care hospital and associated boarding homes in metropolitan Vancouver, B.C., Canada. All patients were administered a structured psychiatric interview (the Present State Examination) and received independent diagnoses of schizophrenia from two clinicians following a review of the interview and hospital records. Each participant satisfied both the *DSM-III* criteria and Research Diagnostic Criteria (RDC) for chronic schizophrenia and had no evidence of neurological disorder (including tardive dyskinesia) or past history of head trauma, had not been treated for substance dependence, and was able to give written informed consent. All patients included in the study provided such consent.

Noncontrast computerized tomography (CT) scans were obtained for all subjects by following CT scanning and measurement procedures outlined elsewhere (7). The CT scan showing the lateral ventricles at their largest was enlarged to 60% of life size and a planimeter was used to calculate lateral ventricle and brain areas. The ventricle-brain ratio (VBR), the ratio of the area of the lateral ventricles to total brain area, served as the measure of lateral ventricle size and was computed without knowledge of test scores or handedness.

The following psychological tests, descriptions of which can be found in *Neuropsychological Assessment*

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TABLE 1. Ventricle Size and Scores on Neuropsychological Tests of 63 Left- and Right-Handed Schizophrenic Patients

	Right-Handed (N=51)		Left-Handed (N=12)		t
Measure	Mean	SD	Mean	SD	(df=61)
Ventricle-brain ratio	6.61	1.98	8.10	2.03	−2.33[a]
WAIS-R					
Full-scale IQ	86.76	11.53	82.08	14.85	1.20
Verbal IQ	91.29	14.49	87.08	17.59	0.87
Performance IQ	84.37	10.59	77.75	10.55	1.95[a]
Wisconsin Card Sorting Test					
Proportion of nonperseverative errors	0.16	0.09	0.24	0.11	−2.88[a]
Proportion of perseverative errors	0.22	0.12	0.22	0.05	−0.13
Number of categories mastered	3.82	1.89	2.75	2.01	1.75[a]
Benton Visual Retention Test					
Number of errors	7.65	4.82	9.50	5.71	−1.16
Finger Tapping Test[b]					
Left hand	41.54	9.84	46.16	8.18	−1.56
Right hand	46.07	10.57	44.20	8.18	0.57
Word Fluency Test					
Number of words generated	34.37	12.54	31.58	16.17	0.66
Auditory Verbal Learning Test					
Number of words recalled	39.64	14.27	41.33	14.75	0.37
Trail Making Test					
Part A completion time (sec)	43.29	12.89	45.45	15.93	−0.48
Part B completion time (sec)	113.98	69.13	133.73	60.60	−0.88

[a] $p<0.05$.
[b] Mean number of finger taps for five trials.

(8), were scored and administered following standardized procedures: 1) the Wechsler Adult Intelligence Scale, Revised (WAIS-R), 2) the Benton Visual Retention Test, Form D, with the background interference procedure, 3) the Word Fluency Test, 4) the Finger Tapping Test, 5) the Wisconsin Card Sorting Test, 6) the Trail Making Test, Parts A and B, and 7) the Rey Auditory Verbal Learning Test. Handedness was determined by writing preference.

RESULTS

Twelve (19%) of the 63 subjects were left-handed. No significant differences were found between the left- and right-handed groups in length of hospitalization, age at onset, medication treatment, and educational level. As table 1 illustrates, the left-handed schizophrenic patients had significantly larger lateral ventricles than the right-handed patients. A Hotelling's T^2 analysis on the psychological test scores revealed an overall significant effect ($F=3.04$, $df=10, 50$, $p<0.01$) and was followed by a series of planned univariate, one-tailed t tests (see table 1) to evaluate our hypothesis that left-handed patients would show impaired performance. Left-handers made significantly more nonperseverative errors and mastered fewer categories on the Wisconsin Card Sorting Test. In addition, they had a significantly lower WAIS-R performance IQ than did right-handers. No other significant differences were found between the two groups. However, inspection of the table reveals that for the majority of the neuropsychological tests, the left-handed patients tended to perform more poorly than the right-handers.

DISCUSSION

To our knowledge, the present investigation is the first to compare the performance of right-handed versus left-handed individuals with schizophrenia on measures of both cerebral morphology and cognitive functioning. Consistent with the findings of Andreasen et al. (5), left-handed patients had significantly larger lateral ventricles. They also had significantly depressed scores on a battery of intelligence and neuropsychological tests. Left-handed patients showed evidence of poor performance on the full-scale IQ and on the Benton, Word Fluency, and Trail Making tests and scored significantly below their right-handed counterparts on performance IQ and the Wisconsin Card Sorting Test.

Data from a variety of sources suggest that schizophrenic patients have a brain dysfunction (9). Silva and Satz (10) have argued that the excess of sinistrality seen in brain-damaged populations is due to early left hemisphere insult, which causes normally right-handed individuals to become "pathological" left-handers. Our findings are consistent with the view that excess sinistrality in schizophrenia is associated with cerebral impairment in that 19% of our sample was left-handed and these individuals showed both neuropsychological and CT scan abnormalities.

Our data do not show an association between left-handedness and left hemisphere disruption, however. Left-handed patients had a tendency to perform poorer than or as poor as the right-handers on a wide range of neuropsychological tasks, regardless of the cortical regions assessed by these tests. Further evaluation of the application of Silva and Satz's hypothesis to schizophrenia could be achieved by using additional neuropsychological tests that may be more sensitive to left hemisphere dysfunction. In addition, it would be of interest to examine the families of left-handed schizophrenic patients who have two healthy parents. If the parents, like their schizophrenic offspring, were more likely to be left-handed, this would suggest that sinistrality in schizophrenia was due more to genetic factors than to brain damage occurring early in life. Investigation of the early medical health of left-handed schizophrenic patients would also be of obvious interest.

Our findings suggest that hand preference might exert a distorting effect in the assessment of the degree of deficit in schizophrenic patients. When studying cerebral function and structure in schizophrenia, therefore, it may be worthwhile to analyze the data from left- and right-handed subjects separately.

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Panic Disorder in Children at High Risk for Depression

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While conventional clinical wisdom has been that panic disorder does not occur in children, evidence derived from structured diagnostic interviews suggests that panic disorder, similar in symptom pattern to the adult disorder, does occur in children and can occur before puberty.

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Conventional clinical wisdom has been that panic disorder does not occur in children (1). Recently, there have been isolated clinical reports on the existence of panic disorder in children (2, 3). However, with the exception of the two cases reported by Vitiello et al. (3), the diagnoses have not been based on structured diagnostic interview.

Although small studies have been conducted (4, 5), to our knowledge there have been no large epidemiological studies of children or adolescents that used *DSM-III* criteria to determine the prevalence of psychiatric disorders, including panic disorder. However, a recent study by Hayward et al. (6, elsewhere in this issue) of 95 ninth-grade high school students found, on the basis of clinical interview, that the lifetime prevalence of four-symptom panic attacks was 11.6%. Epidemiological studies of adults who retrospectively reported their age at onset of panic disorder suggest that onset of panic disorder can be quite early. Results from the National Institute of Mental Health Epidemiologic Catchment Area Study showed a peak onset of panic disorder between the ages of 15 and 19 years, with onset before puberty in some cases (7).

Retrospectively taken childhood histories of adults with panic disorder, studies of the parents of children with anxiety disorders, and studies of children with depressed and anxious parents lend support to an association between adult and childhood forms of anxiety disorders. Specifically, studies of adults with panic disorder have found cases of onset of panic disorder in childhood or early adolescence (8).

This paper presents symptom and diagnostic data on seven children with panic attacks. Six of these children met *DSM-III* criteria for panic disorder on the basis of direct, structured diagnostic assessment with the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Life-Time Version (Kiddie-SADS-L).

METHOD

The subjects were part of a study of 220 children, ages 6 to 23 years, who were at high or low risk for depression by virtue of their parent's diagnosis. Children of depressed parents were matched by age and sex to children of nondepressed parents. Detailed methodology is presented elsewhere (9). Because this study determined age at onset of psychiatric disorders on the basis of retrospective report, subjects included individuals up to 23 years of age. Subjects and their parents were interviewed separately with the Kiddie-SADS-L during the initial assessment by a trained interviewer with clinical experience. At 2-year follow-up the children were interviewed again with the Kiddie-SADS-L. *DSM-III* diagnoses of children were made by a child psychiatrist and a child psychologist on the basis of all available information from both interviews, as well as school and psychiatric records where available; the child psychiatrist and psychologist were blind to the parents' clinical condition. Agreement between the psychiatrist and psychologist was excellent (kappa= 0.69 for anxiety disorders in the 220 children) (10).

RESULTS

Of the 220 children, four girls and three boys, who ranged in age from 11 to 23 years at the time of initial assessment, were found to have panic symptoms (see table 1). Six of the seven children met the criteria for panic disorder. One child did not have panic attacks with sufficient frequency to meet the diagnostic criteria. The age at onset of panic disorder ranged from 5 to 18 years. In four cases onset was before puberty.

During the first interview, four of the children recalled panic symptoms, all of which had occurred

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TABLE 1. Age, Age at Onset, Symptoms, and Comorbidity in Seven Children With Panic Symptoms

	Patient						
Item	1	2	3	4	5	6	7
Age (years)							
At second interview	17	20	11	18	23	14	11
At onset of panic	9	18	5	10	12	13	6
Sex	M	F	M	F	F	F	M
Symptoms							
Shortness of breath	+	+	+	+	+	+	+
Palpitations	+	+	+	+	+	+	
Chest pain	+	+		+	+		
Choking		+		+	+		
Dizziness		+		+	+		
Sweating		+		+		+	
Trembling			+		+	+	
Fears of death	+		+		+	+	
Faintness	+		+	+	+		
Feelings of unreality				+		+	+
Tingling					+		+
Hot and cold flashes					+		
DSM-III diagnoses							
Most common							
Panic disorder		+	+	+	+	+	+
Major depression	+	+		+	+	+	
Separation anxiety disorder	+		+	+	+		+
Total	5	4	5	3	3	2	2

within 1 year of the interview, and five of the parents reported previous panic symptoms in their children. During the follow-up interview, two of the subjects were still experiencing panic attacks. Only subjects who were currently symptomatic reported panic symptoms at the follow-up interview.

Symptoms were similar to those found in adults with panic disorder (see table 1). Feelings of panic, anxiety, or fear occurred suddenly and were accompanied by multiple physical and psychological symptoms. All of the children reported shortness of breath, and the majority had palpitations. Symptoms reported by half of the subjects included sensations of chest pain, choking, dizziness, sweating, trembling, or fainting; fears of death; and feelings of unreality. The mean number of symptoms for each subject was 6.1.

All of the children had other diagnoses, most commonly major depression and separation anxiety disorder. The onset of panic disorder either occurred in conjunction with separation anxiety disorder or major depression or followed the onset of separation anxiety disorder by at least several months. Although several of the subjects used illicit drugs and alcohol, only one met the criteria for substance abuse. Four of the seven children had at least one parent with panic disorder in addition to depression. All cases of panic disorder were found in the children at high risk for depression; no cases were found in the children of nondepressed parents.

DISCUSSION

The findings suggest that panic disorder does occur in children and can occur before puberty. The symptom pattern and high comorbidity with major depression are similar to those found in adults. It must be noted that the children we studied did not represent a probability sample of a community. Because panic disorder occurred in the children of depressed parents and not those of nondepressed parents, the frequency with which the disorder occurred is probably exaggerated.

In this study we used the child psychiatrist's and psychologist's best estimate, based on multiple sources of information, to determine the child's diagnosis. Agreement between psychiatrists was excellent. There were discrepancies between parents' and children's reports, however. Parents were more consistent than the children in reporting past episodes of panic. Of the four children who reported panic symptoms, all either were experiencing symptoms at the time of the interview or had experienced symptoms within a year of the interview. The children were able to report the phenomenology of panic attacks when they were symptomatic, but in their retrospective reports they failed to note past panic episodes that the parents reported.

These findings, if replicated, would suggest that systematic assessment of panic disorder should be part of a general psychiatric workup of children, particularly children at risk by virtue of depression in the parent. A host of questions remain. We do not know the continuity of childhood panic disorder into adulthood, the clinical course or its impact on development, or the actual prevalence. While there is good evidence for the efficacy of pharmacologic and behavioral treatment of panic disorder in adults (11), the efficacy of these treatments in children is unknown.

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Panic Attacks in Young Adolescents

Chris Hayward, M.D., M.P.H., Joel D. Killen, Ph.D., and C. Barr Taylor, M.D.

The lifetime prevalence of interview-determined four-symptom panic attacks in 95 ninth graders was 11.6%. Those with panic attacks were significantly more depressed, were significantly more likely to have separated or divorced parents, and tended to be more likely to have tried cigarette smoking.

(Am J Psychiatry 1989; 146:1061–1062)

Although adults with panic attacks often report experiencing their first panic episode during adolescence (1), little is known about the frequency of panic attacks in this age group. Moreau et al. (2, elsewhere in this issue) have described six cases of panic disorder that began in childhood and adolescence; however, there have been no population-based studies of panic attacks in adolescents (3). In this study, we interviewed a sample of ninth graders to determine the prevalence of panic attacks in young adolescents. We also explored the relationship between panic attacks in adolescents and both substance use and depression.

METHOD

Ninth-grade students (N=106) from three physical education classes in a suburban high school near a large northern California city were asked to complete a survey questionnaire and participate in a structured psychiatric interview. The racial composition of the school is 59.8% white, 21.2% Asian, 15.0% Hispanic, 3.3% black, and 0.7% other. Three classes were randomly selected from a total of six physical education classes in the ninth grade. Passive consent was obtained from the parents and written informed consent was obtained from the students.

The questionnaire included questions about ethnicity, parents' marital status, and substance use and the depression scale from the SCL-90-R (4). Cigarette smoking, marijuana use, and alcohol use were categorized as "never used," "experimental use" (use of the substance less than once a week), and "regular use" (use of the substance weekly or daily).

Interviews lasting 5–15 minutes were conducted privately by a psychologist or a doctoral candidate in psychology who used the panic disorder section of the Structured Clinical Interview for *DSM-III-R* Disorders (SCID) (5). Only the panic section of the SCID was used because of the time limitation in the classroom. If a student responded affirmatively to the SCID screening question about sudden fright, the interviewer then determined if the fright was spontaneous and not due to phobic stimuli (social or simple) and did not occur in situations in which most people might experience some fear or autonomic stimulation, such as when taking an examination or during exercise. If so, the interviewer proceeded with the other SCID questions about panic attacks. The primary investigator (C.H.) later determined if the subject had experienced a panic attack as defined in *DSM-III-R*. Possible medical conditions and drug use associated with panic attacks were not assessed.

Ninety-five of the 106 students who received the questionnaire also participated in the structured psychiatric interview. Because of the time constraints of class periods, 11 students were not interviewed. The completion rates for those who both received the questionnaire and were interviewed (N=95) were 98% (N=93) for the substance use questions and 82% (N=78) for the SCL-90-R depression scale. Of those interviewed, 52% (N=49) were boys and 48% (N=46) were girls; their mean age was 14.5 years (range, 14–16). With respect to ethnicity, 48.4% identified themselves as white, 20.0% as Asian, 14.7% as Hispanic, 6.3% as black, 3.2% as Native American, and 5.4% as other (total=98%; some subjects did not answer question).

For data analysis the sample was divided into those who had experienced a panic attack, including a symptom-limited attack (which has fewer than four symptoms), and those who had not. Chi-square analysis with Yates' correction was used to compare the two groups with respect to substance use; experimental and regular users were combined for this analysis.

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TABLE 1. Substance Use and Parental Divorce or Separation Among Ninth Graders With and Without Panic Attacks[a]

Variable	Panic		No Panic	
	N	%	N	%
Cigarette use[b]				
Never used	3	23	42	53
Experimental or regular use	10	77	38	48
Marijuana use				
Never used	8	61	54	68
Experimental or regular use	5	39	25	32
Alcohol use				
Never used	3	23	13	17
Experimental or regular use	10	77	65	83
Parental separation or divorce[c]				
Yes	8	61	22	29
No	5	39	54	71

[a] Not all adolescents answered every question on the questionnaire.
[b] $\chi^2=2.8$, df=1, $p<0.10$.
[c] $\chi^2=3.9$, df=1, $p<0.05$.

Group differences in marital status of the parents were also tested with Yates-corrected chi-square analysis. The Student's t test was used to test for group differences on the depression scale of the SCL-90-R.

RESULTS

Those who experienced at least one four-symptom panic attack constituted 11.6% (N=11) of the sample (N=95), 17.4% (N=8) of the girls and 6.1% (N=3) of the boys. An additional 3.2% (N=3) of the sample, all boys, reported experiencing at least one symptom-limited panic attack. Thus, there were 14 students who had experienced a panic attack of any kind and 81 who had not. As indicated in table 1, significantly more of the panic attack group than the no panic attack group had parents who were divorced or separated; in addition, there was a tendency for more of the panic attack group than the no panic attack group to have tried smoking cigarettes, and there were no significant differences between the groups with respect to marijuana use and alcohol use. The panic attack group had significantly higher mean±SD scores on the depression scale of the SCL-90-R (1.4±0.8, N=13) than the no panic attack group (0.82±0.7, N=65) ($t=2.6$, df=76, $p<0.05$).

DISCUSSION

The results of this study confirm that panic attacks are not confined to adults. The 11.6% lifetime prevalence rate of four-symptom panic attacks we observed in adolescents is high compared with the 9.7% lifetime rates for panic attacks in adults found in the Epidemiologic Catchment Area Program study (6). Other population-based studies have reported prevalence rates between 11% and 35% for panic attacks in adults (7–9). Telch et al. (unpublished paper), using a questionnaire, assessed 2,375 college students and observed that approximately 12% had experienced unexpected panic attacks in their lifetimes. Clearly, the observed frequency of panic attacks varies according to the method of assessment, number of symptoms required for the diagnosis, time period considered, and the population studied. Caveats in interpreting the prevalence rate we found include the possible recall bias in the assessment of lifetime prevalence rates and the as yet unstudied comparability of a shortened interview with the standard structured diagnostic interview.

In children and in adults there is considerable comorbidity between anxiety and depression (10). The significant association that we found between panic attacks in young adolescents and a self-report measure of depression suggests that panic attacks and depression probably overlap in adolescents as well. Future community-based studies of panic attacks in adolescents should formally assess depression to better distinguish between these two disorders.

The finding that the parents of those having experienced a panic attack are more likely to be divorced or separated is consistent with a theory of panic attacks which suggests that early loss, or sensitivity to separation, may be a risk factor for the later development of panic attacks. We do not know the temporal relationship between the parental separation and the reported panic attacks in this study.

We also found a possible association between cigarette smoking and panic attacks. Panic attacks may predispose adolescents to smoke cigarettes, or, alternatively, smoking withdrawal may have triggered panic episodes. With respect to the negative finding regarding alcohol use, ninth graders may be too young to exhibit the frequently observed relationship in adults between anxiety disorders and alcohol abuse.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

AUTOBIOGRAPHY, BIOGRAPHY, AND HISTORY

Can You Hear the Clapping of One Hand? Learning to Live With a Stroke, *by Ilza Veith. Berkeley, University of California Press, 1988, 98 pp., $15.95.*

When the distinguished Oxford professor of medicine Sir George Pickering published *Creative Malady* (1), he included among those men and women whose illnesses had spurred their creative work Charles Darwin, afflicted with an affective disorder, Marcel Proust, who suffered from asthma, Sigmund Freud and his neurosis, and other notable individuals. Were Pickering alive today my guess is that he might want to include additional examples of the remarkable convergence of creativity and illness. Surely he would be fascinated to read about Ilza Veith's heroic battle with a physically debilitating stroke and to include her case as well.

A medical historian by profession, Dr. Veith has held professorships at Johns Hopkins, the University of California, the Menninger Clinic, and elsewhere. Interested since childhood in the Orient, she has become world renown for her contributions to the understanding of Chinese medicine, including acupuncture therapy. On March 28, 1963, while on a lecture tour, Dr. Veith slipped and fell, severely injuring her left leg. Exactly 1 year later, on March 28, 1964, she suffered another, much more serious "accident."

> As I usually did once a month, I decided to palpate my breasts as a precautionary measure . . . . I palpated thoroughly with my right hand, first feeling my left breast and axilla. After completing that part of the examination I tried to lift my left arm in order to palpate my right breast. To my utter bafflement I found myself unable to do so. Not even a finger could I move. (p. 16)

It was hemiplegia. Dr. Veith's book discloses in eloquent detail what it is like to discover oneself thus disabled, the terror of the diagnostic process, how stroke patients are treated, and her amazing adaptation to such a calamity. Ironically, she had been working at the time on a major piece of research into hysteria (2). Her exceptional powers of observation, her sensitivity to psychological and emotional aspects of disease, her wit, and her ability to communicate medical concepts in clear, precise language make this an outstanding volume, something of value for physicians and patients alike.

Dr. Veith describes the dreams associated with her disability, how it affected her career, and the reactions of her colleagues, friends, students, and above all her husband, to whom the book is dedicated. Hans Veith assumed many of Dr. Veith's household and social responsibilities, found innovative ways to assist with her work as a teacher and scholar, and helped her to navigate, even to travel and resume her very active career. Especially interesting for the psychiatric reader are Dr. Veith's insights into the affective components of brain disease, the loss of control over emotional expression, the sudden involuntary outbursts of laughter or crying, and the "abreactions" at unexpected moments. One chapter, "The Hospital: Tender Loving Care?" discusses the mistakes that physicians can easily make by being intrusive, officious, or simply uninformed. Psychotherapy was something Dr. Veith did not welcome when it was offered to her without her request, but she benefited from it when she sought it informally from friends and colleagues she could trust.

She also writes about the effects, both good and bad, of surgical approaches and physiotherapy and comments in a disarming way on practical issues such as the stroke victim's need to relearn habitual movements such as standing up and sitting down, walking, feeding oneself, and getting in and out of automobiles. In "Afterthoughts" she reveals her thoughts about aging and retirement, her anxiety concerning dependency on her husband, and her stoicism in the face of a permanent disability: "I do not complain to anyone; it is only my emotional solitude that is sensed by others and is sometimes resented, since it is interpreted as a rejection and evokes a remoteness that leads to estrangement" (p. 92).

This little book—a humble disclosure of what it is like to endure major disease, to be both a patient and a clinical observer, and to preserve one's integrity in the face of a medical disaster—cannot be praised highly enough. Most strongly recommended for chronically ill patients and their therapists, it is also a book for students and the general reader.

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Vital Involvement in Old Age: The Experience of Old Age in Our Time, *by Erik H. Erikson, Joan M. Erikson, and Helen Q. Kivnick. New York, W.W. Norton & Co., 1986, 352 pp., $19.95; $8.95 (paper).*

This book consists of four parts: 1) a description of the life cycle stages according to Erik Erikson, 2) life historical data exemplifying these stages in 29 octogenarians, 3) an analysis of Bergman's film *Wild Strawberries,* which depicts the life stages of Professor Borg and his coping with disengagement and involvement, and 4) an assessment of the coping strategies in our society. The sample of octogenarians on whom the bulk of the book is based were the parents of children included in the Guidance Study of the Institute of Human Development of the University of California, Berkeley. The eight stages that constitute the Eriksonian framework are the well-known sequence of infancy, early childhood, play age, school age, adolescence, young adulthood, adulthood, and old age. Two of the authors are in their 80s, and the third seems to be in her 30s.

The general theme of the book is to portray what vital involvement in old age consists of. It is a provocative appeal to the elderly to have vital involvement during their old age despite the many obstacles that stand in the way, leading to withdrawal or disengagement. I found the book fascinating and read it like a novel at first, not permitting any critical thoughts to interfere with the beautiful literary portrayal of the life histories of successes and failures in the 29 octogenarians. These are described in the chapter entitled "The Voices of Our Informants" and the chapter giving the life history of Professor Borg, the protagonist in *Wild Strawberries*. I advise readers to follow this plan and let themselves be absorbed in the beautifully detailed, often dramatic life histories.

To assess the book as a contribution to knowledge rather than as a literary production is very difficult, however, because the only frame of reference is the Eriksonian concept of stages and any attempt to contrast the results with those obtained by using any other criterion becomes well-nigh impossible. The last stage of the life cycle, which is the main focus of the book, involves ego integrity versus despair and disengagement. Erikson's is a humanistic, intuitive approach to aging in terms of psychosocial variables to the exclusion of biological factors. This introduces a relativity factor, since the role of the environment seems supreme, permitting only cultural influences to determine the behavioral outcome. Consequently, we cannot expect the authors' findings to hold true in all cultures because of the great variation from culture to culture in the treatment and care extended to the aged, especially when Eastern and Western cultures are contrasted. Although the role of psychosocial factors in aging is of great importance, the omission of consideration of biological factors is bound to provide obstacles to the general acceptance of the view presented.

I found an astonishing surprise on opening this book. I had expected another guide to old age. Instead, it was as if while threading my way through an overgrown rain forest I suddenly came upon a clearing in which a beautiful cathedral was erected in the middle of the jungle. This is how I felt on entering the humanistic psychosocial world that the Eriksons and their younger collaborator erected to describe the aging process and its significance for the life cycle.

On closer examination of the jungle of gerontology, it became clear that lesser shrines have been built earlier for devotees. Among these are Shakespeare's stages of life, the Talmud's age sequences, Cicero's cogitations, and many others to which historians may someday turn their attention. None, however, had the magnificence and grandeur of the structure of these authors. Even Freud and Piaget occupy only antechambers in this edifice, and several smaller altars have been added by contemporaries like Levenson, Pollock, and Gould (to mention only the most recent).

The authors describe the main thesis of the book as follows:

> Here we intend to follow through only this one trend, namely, the eight stages of psychosocial development, which produce the strengths necessary for a mutual involvement in an ever-increasing social radius, from infancy through adulthood and into old age. And this is our basic interest in this study: the remaining or new potentials of the last interactions and the vital (if paradoxical) involvement in the necessary disinvolvements of old age.

In contrast to the diatribe against old age voiced by the chorus in Sophocles's *Oedipus at Colonus*, the authors of *Vital Involvement in Old Age* provide a hopeful, even idyllic description of the end to life despite the potential ravages of decline in function. Surprisingly, the span of life in the eras of Sophocles, Cicero, and Shakespeare was probably only half or less of what it is now. Perhaps the shortness of the life span led to the pessimistic view of old age by the ancient writers and Shakespeare ("Sans teeth, sans eyes, sans taste, sans everything"—*As You Like It*, Act II, scene vii, line 173).

A careful examination of the cathedral itself leads to surprising findings. It is like a castle built on air, without touching the fundamental biological foundations required for a scientific grasp of its underpinnings. This is not to denigrate the value of the book but, quite the contrary, to indicate how remarkable it is to have reared a magnificent structure unanchored in the biological substrate of existence. The book reads like a novel, with fascinating case history anecdotes selected to exemplify the conflicting trends that exist at each stage of development—the dynamic balance of opposites that are formulated as syntonic and dystonic vital involvements by the authors. This leads to a resolution that depends on their judicious balance: 1) infancy—trust versus distrust, leading to hope, 2) early childhood—autonomy versus shame or doubt, leading to will, 3) play stage—initiative versus guilt, leading to purpose, 4) school age—industry versus inferiority, leading to competence, 5) adolescence—identity versus confusion, leading to fidelity, 6) young adulthood—intimacy versus isolation, leading to love, 7) adulthood—generativity versus self-absorption, leading to care, and 8) old age—integrity versus despair, leading to wisdom. To be sure, the attempt to relate each anecdote to an underlying stage theory is sometimes a tour de force, but the entire argument is usually quite convincing.

The task of reviewing such a literary production is beyond the capacities of one who wanders into this field with the limitation of a biometric background. However, if one needed a defense for the humanistic approach as opposed to the biological, it could be found readily in the words of Rene Dubos and S.J. Gould. According to Dubos, all the processes found in living things, including humans, obey the laws of inanimate matter, an assumption that even the early Freud lived by. Dubos also says that all these forces are merely the stage props for the drama we enact on the stage of life. Perhaps the most important determinant of our behavior has been overlooked—our ability to be a self-starter, to paraphrase Dubos. Unlike other organisms that are shaped by their environment through accommodation, we humans shape our own exogenous and endogenous environment through assimilation as well as accommodation. S.J. Gould says that it is the interaction between the wired-in portion of the brain and environmental forces (especially the psychosocial) that determines our behavior. These internal structures are not transmitted genetically, however, but culturally through the neuroplastic portion of the brain rather than through the wired-in portion.

In the field of cognitive psychology, such terms as will, imagery, hopefulness, optimism, guilt, and shame were banished by behaviorism but have now been resurrected. The current progress in the field promises that the seminal insights of the authors of *Vital Involvement in Old Age* may eventually be attached to the corpus of certitude that we call science, albeit with suitable modification to fit the framework of science. Thus, the artistic humanistic approach may yet be vindicated, for, according to Leonardo da Vinci, "Art is the root of all science."

Perhaps the authors could have avoided their extreme dependence on the theory that psychosocial forces alone produce maladaptations by appealing to the concept of vulnerability, which encompasses the idea that there are both biological-genetic and psychosocial factors in maladaptation. This might have lent a more balanced view of developmental theory.

One wonders how the Eriksonian stages would compare with the Piagetian. Piaget also posits eight stages, but he ends with age 18, by which time presumably all the foundations for development have been laid down. And what about Levensonian, Gouldian, and other frameworks? In a search of all the articles on aging in the *Annual Review of Psychology* during the last decade, I found Erikson's name only four times. Datan et al. (1) referred to a conflict between a mature adult student and his professor who both shared the same stage of development (generativity) chronologically but differed in their experiential backgrounds. Markus and Wurf (2) cited Erikson in an article that dealt primarily with self-identity. Showers and Cantor (3) cited Erikson in an article that dealt with life cycle changes. The fourth citation was made by Kranz et al. (4), who discussed the role of inferiority (school-age stage) and efforts to establish identity (adolescence stage) as factors in the initiation of smoking behavior. Perhaps *Vital Involvement in Old Age* may accelerate interest in the Eriksonian system.

The question also arises as to whether stage theories are as useful as theories that arise from considerations of quality of life, turning points not related to established stages, life styles, or a single ubiquitous theme in which a continuous direction of development seems to emerge.

In summary, this volume, despite its somewhat disembodied *luftmensch* quality, is a most entrancing description of how one system views mankind's struggle for vital involvement against the inroads of disengagement in old age. Anyone interested in old age professionally or personally can hardly afford to overlook it.

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Different Drums: A Doctor's Forty Years in Eastern Africa, *by Michael Wood. New York, Crown, 1987, 223 pp., $24.95.*

Of all the continents, Africa still seems the most mysterious, its past, present, and future the hardest to understand. Perhaps in part due to that perception, more and more Americans and Europeans seem to be selecting it as a travel destination. It is by now easy to find travel guides that provide sufficient information on African countries for the average tourist, but for the person seeking a deeper understanding of the countries, their history, and their culture, helpful books are harder to find. For health care professionals interested in visiting Africa—or people just looking for a better understanding of what is happening there from a medical point of view—*Different Drums* not only provides an excellent overview of the complex health problems of Eastern Africa but also offers insights into the recent history, the present complex state of affairs, and the uncertain future of this continent, along with a fascinating account of the author's unique medical career in Africa.

Born and trained in Great Britain, Michael Wood spent 40 years in Africa practicing medicine and surgery. In this book he shares his experiences and ideas about the people and the cultures he encountered. He lets us participate in the excitement of his decision to expand his reach by learning to fly and establishing the Flying Doctors Service and AMREF, a large international organization providing emergency medical and communication services as well as education to a growing number of Eastern African and Central African countries. The reader shares Dr. Wood's adventures, such as getting lost in a small plane in the incredible vastness of the African desert. We share his feeling of being overwhelmed by the immensity of the medical problems facing the physician in Africa, and we share such personal stresses as being forced to sell a prospering farm in the foothills of Mount Kilimanjaro to the government.

For psychiatrists, several chapters describing Africa's indigenous healers and their practices, illustrated with superb and brilliant large color photographs by David Coulson, are particularly interesting. Even when describing rather bizarre-sounding procedures, such as the live burial of a psychiatric patient with a goat for up to an hour in a mound of earth (the goat is supposed to die and the patient is supposed to be cured after having displaced his or her evil spirits onto the goat), Dr. Wood maintains the detachment of an anthropologist and at the same time the warmth and humility of an old-fashioned family practitioner. He is well aware of the discrepancy between the very meager resources and the almost overwhelming immensity of the problems presented to the healer in Africa—whether Western-trained physician with inadequate technical supplies or indigenous healer in a changing system of cultures and beliefs. He examines the devastating effects of overpopulation, overgrazing, deforestation, drought, and soil erosion, yet he ends the book on a hopeful note:

> Laurens von der Post tells a story: There was a bushman who was visited by three daughters of the gods. He chose the most beautiful and married her. She brought with her a box, with strict instructions that this was her gift to the bushman, but that he must never look into the box. Of course curiosity finally overcame him and he opened the box; there was nothing inside. The girl immediately disappeared and never returned. Thus he was punished, not because he disobeyed and looked, but because he could not see what was inside; he could not see what she had brought.
>
> The reality which ancient man saw and expressed to the world of his day is still present with us. It is woven into the reality of the present. As we look into the treasure box of Africa we can see its richness shining through the myriad threads of present-day life, illuminating our reality with the originality and inspiration of the early soul of man.

The reader will find *Different Drums,* with its magnificent full-page color photographs and its interesting mixture of adventure stories and ideas about civilization, medicine, and life in general on this mysterious continent, a little treasure box in itself that, in contrast to the box in the story, will yield its treasure freely to the reader.

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Psychohistory: Readings in the Method of Psychology, Psychoanalysis, and History, *edited by Geoffrey Cocks and Travis L. Crosby. New Haven, Conn., Yale University Press, 1987, 318 pp., $37.50 (paper).*

On the night before Christmas Eve 1888, Vincent van Gogh severed the lower half of his left ear and presented it to a prostitute he knew, with the request that she "keep this object carefully."

This mad act, fearful and enigmatic, is perhaps as famous as Van Gogh himself. Yet, within the limits of undiluted science, psychiatry can offer precious little to explain it. We could categorize it as pathological self-mutilation in a psychotic affective disorder of uncertain etiology. We could classify it epidemiologically, comparing the relative rates of self-mutilation for personality disorders, factitious disorders, mental retardation, and psychotic disorders. We could hypothesize biological explanations in endogenous opioid release or "stimulation hunger" (1). But, finally, we must acknowledge that the explanatory power of pure science fails our very human need to understand the basis for Van Gogh's self-mutilation.

However, if we expand our concept of science through what Karl Jaspers called understanding (*verstehende*) rather than explaining (*erklärende*) psychology, we may attempt to understand Van Gogh's act symbolically, indeed historically, in ways with untestable and unasserted predictive power. Doing so, we risk our claim to science in a search for meaning in what is otherwise elusive.

By definition, the editors of this volume have chosen to explore the latter, psychohistorical approach to major historical events and figures. Their collection will intrigue both the faithful and the skeptic alike. Refreshingly, no single psychohistorical method holds sway in this collection; all are suspect, from the high-church analytic to the trait-tracing psychological. Indeed, the most intellectually challenging offerings are relentlessly critical of the very project of psychohistory. H.J. Eysenck's witty and insightful 1953 essay, "What Is Wrong With Psychoanalysis?" remains fresh reading today, and Robert Coles's "On Psychohistory" showcases every pitfall awaiting the psychohistorian since Freud presented his careful yet daring portrait of Leonardo da Vinci in 1910 (2). (The editors of the *Standard Edition* [2, p. 60] cautioned that Freud's portrait was not the first application of psychoanalytic principles to historical figures and referred to the work of Sadger in 1908 and 1909.)

Professor Coles decries the romance of the key: the word or idea that, like the "Rosebud" of cinema's *Citizen Kane,* magically unlocks the secret of the hero's heart, as though artists, intellectuals, and heads of state all spring upon the world stage driven by a single inner conflict. Psychohistory's fixation on psychopathology in the genesis of accomplishment strikes Coles as both unscientific and unrealistic. Why should the disorders that shackle our psychiatric patients produce such formidable accomplishments when uncovered in the famous or infamous? Why are psychohistorians far less concerned with the healthy determinants of greatness (intelligence, courage, activity), which are so much more uncertain in our science, than the pathological, which so predominate?

Coles, in turn, receives formidable rebuttal in an essay by Joseph Woods, a historian. Woods perceives, as does personality theorist Theodore Millon (3), a fundamental error in psychiatry's emphasis on pathology as opposed to personality structure in understanding narcissism, the acknowledged hallmark of the historical figure. Woods and Millon see narcissism not as the bedrock of crime and personality disorder but as a continuum, from the failed narcissist—on drugs, the couch, or in prison—to the successful narcissist at the historical helm. With an array of examples from Stalin to Hitler, Woods shows how master politicians actualize their grandiosity through a relentless self-seeking that is unencumbered by guilt or sentiment and indifferent to truth, principle, and the rights and humanity of others at the same time they manipulatively portray themselves as servants of the very values they ignore and their followers obey. In Woods's psychohistory, an ounce of Machiavelli outweighs a pound of Freud.

Where does all this leave the mutilated Van Gogh? No fewer than 13 explanations, most of them psychodynamic, are suggested as possible motivations. Examples include the turning inward of rage against his friend Gauguin, the emulation of a bullfighter offering a bull's severed ear to the lady of his choice, and a practical, pitiful attempt to escape hallucinated voices. This last is among the rare references to Van Gogh's psychiatric illness, alternately termed a psychotic state and a delirium.

Psychiatry is obliged to suffer such lapses gladly. Unique among the medical specialties, we may gratefully number among our basic sciences the entire spectrum of disciplines that seek to understand the human condition. Although hybrid ventures such as psychohistory are at greater risk for intellectual and scientific sterility, to the embarrassment of their more rigorous progenitors, they define fascinating questions even when they can only hope to provide answers. If one is not daunted by such caveats, this collection will assuredly prove worthwhile.

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Racial Hygiene: Medicine Under the Nazis, *by Robert N. Proctor. Cambridge, Harvard University Press, 1988, 414 pp., $34.95.*

The revelations of atrocities committed by German scientists and physicians under the Nazis before and especially during World War II so terrified Western civilization that even now, nearly 45 years after the close of the war, we are only beginning to progress from recounting, judging, and, almost instinctively, disowning these events to slow, tentative attempts to understand them.

In *The Nazi Doctors* (1), Robert Lifton discussed the psychology of the SS physicians who participated in mass murder of supposedly defective and racially inferior human beings. He emphasized the institutionalized Nazi medical model of healthy and diseased races. In fascinatingly detailed case histories of SS physicians, Lifton introduced the concept of doubling: the formation of a second, autonomous self able to perform acts that the primary self need not condone or even contemplate.

Lifton's concept of doubling is intriguing, but one must consider whether it is, in fact, yet another effort to disavow the reality of the extremes of human capabilities, bypassing the simpler wisdom of Terence's dictum, "I am a man, and reckon nothing human alien to me" (*Heauton Timoroumenos,* 25).

In *Racial Hygiene,* Robert Proctor proposes no new intrapsychic mechanism to explain the history of German medicine under Nazism. His view, amply documented by extensive research into German medical literature of the period, is that such practices as involuntary sterilization, euthanasia, medically and scientifically sanctified racism, ethnocentrism, and genocide were outgrowths, indeed applications, of then internationally current beliefs in eugenics and social Darwinism.

The Nazi movement itself is revealed as deeply grounded in a quasi-scientific belief system of naive genetic determinism espousing the heritability and invariability of all human characteristics. This one-sided view of the nature-nurture dichotomy is perhaps best revealed in the classic assertion that "National Socialism is nothing but applied biology." Again and again Proctor reproduces or quotes Nazi literature and propaganda recommending itself as medically factual and medically endorsed: politics authenticated with the imprimatur of science.

But in this the Nazis were not alone. The competing totalitarian regime in Russia was equally grounded in its own strictly environmentalist doctrine of Lamarckism and Lysenkoism. Even in the face of contrary evidence, Soviet science accepted as proven fact the heritability of acquired characteristics, assuring its compatibility with a Marxist vision of class struggle.

Apparently a layman, Proctor is medically informed. He reviews German eugenics, genetics, and epidemiologic research in the Nazi period, including identical and fraternal twin concordance studies for the heritability of, among other things, tubercular infection, memory, cancer, and divorce. Discussed at length is the Kaiser Wilhelm Institute for Anthropology, Human Genetics and Eugenics, established under the Weimar Republic in 1927, which provided graduate training for Josef Mengele, M.D., Ph.D., and housed the "scientific materials" he acquired in his now notorious work at Auschwitz.

Notably absent, regrettably for the medical reader, is a critical scientific evaluation of the materials reviewed. Although Proctor's research is clearly first-rank, he repeatedly skims or skirts areas where reasoned scientific review of the many studies summarized might further our understanding of the subtle ways in which political duty or preconceptions may compromise scientific objectivity. Similarly, Nazi "medical" experimentation, which even recently has been the subject of renewed debate, is covered in a few brief pages. The moral and ethical questions surrounding involuntary human experimentation are never addressed or even posed.

These are perhaps questions of scope rather than scholarship. Such discussion may not be of moment to the lay reader, to whom this volume is ostensibly addressed. For those of us in psychiatry, Mr. Proctor has explored very timely issues. In a period when U.S. psychiatry is reevaluating environmental and social learning theories and genetics and biology are emerging as pivotal to our understanding of psychiatric illness, this book may well serve as a warning of the dangers inherent in the ready biologizing of social and psychiatric aspects of medical science.

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HUMAN COGNITION

The Exceptional Brain: Neuropsychology of Talent and Special Abilities, *edited by Loraine K. Obler, Ph.D., and Deborah Fein, Ph.D. New York, Guilford Press, 1988, 512 pp., $39.50.*

In this volume the authors take on the formidable challenge of addressing what is known about the neuropsychological underpinnings of talent and special abilities. Five questions are posed in the introduction: 1) Is there a neurological substrate for talent? 2) What portions of the brain are most responsible for the mediation of talent? 3) What accounts for the difference between the neurological substrate of talented versus untalented persons? 4) What cognitive psychological processes are associated with the expression of the neural activity of the talented individual (e.g., speed of performance, quickness of automatization)? and 5) How should talent be investigated from a neuropsychological perspective? These are worthy questions.

The book is divided into four sections, each with several chapters. The first section offers a survey of specific areas of talent and includes chapters on calculating prodigies, mathematical talent, hyperlexia, acquisition of a second language, music, chess, superior memory, and eidetic imagery. The second section provides a series of case reports of individuals with exceptional abilities. The third section presents information from group studies of drawing abilities, acquisition of grammar, and the association of special abilities with juvenile manic-depressive illness. The final section includes several overviews of some of the principal themes of the book, such as the occurrence of special abilities in autistic children and the role of practice in the development of exceptional abilities.

There are several particularly rich and informative chapters. The chapter by Lee Cranbery and Martin Albert on the "chess mind" stands out as particularly provocative and illuminating. They note that chess champions tend to be young Jewish men with a talent for mathematics as well as chess and that a disproportionate number have come from the Soviet Union. The authors propose a comprehensive neurosocial theory capable of explaining many of their observations. They draw on the late Norman Geschwind's hypothesis that testosterone exposure in utero slows growth of the left hemisphere and leads to a relative acceleration of right hemispheric development, providing a neural substrate for superior right-brain-mediated abilities in males. In the Soviet

Union, there have been relatively few opportunities for Jews to demonstrate excellence in competitive pursuits, and the quiet devotion to chess has provided such a forum. Thus, endocrine, neural, religious, and political forces converge to explain the seemingly paradoxical features of chess champions. Cranbery and Albert provide supportive data for their hypothesis of right hemispheric mediation of chess abilities, including a higher prevalence of non-right-handedness among chess players (predicted by the Geschwind theory) and relative preservation of chess ability following left hemispheric brain injuries. This chapter offers a model approach to the study of the neurology of creativity and talent.

The chapter by Tedd Judd on "The Varieties of Musical Talent" is a clever exposition of neuropsychomusicology. Judd reviews left and right hemispheric contributions to musical abilities and develops a catalog of neuropsychological skills subserving different aspects of musical engagement. He reviews the relationship of music to vision, hearing, and general intelligence to provide insight into the neurophysiological context in which musical talent develops. Judd also briefly reviews the results of focal lesions on musical abilities and concludes that the consequences of local injury have been too variable to allow generalizations regarding the role of specific hemispheric regions in musical ability. I suspect that other authors would make much more of these case studies, which are usually interpreted as supporting a role for the right hemisphere in pitch and timbre and for the left hemisphere in rhythm. Judd concludes by drawing attention to the central role of musical memory in musical talent.

The contributors to the book hold remarkably discordant views regarding the basic nature of exceptional abilities. Most state or imply that gifted individuals have a unique neurophysiological organization that allows them to develop specific abilities to an exceptional degree. Ericcson and Faivre, however, develop the rather extreme view that there is no acceptable evidence for special aptitudes and that exceptional abilities arise from extensive practice. Their position may reflect in part their rather impoverished list of exceptional abilities—"mental calculation, absolute pitch, speaking backwards, and memory for verbatim information and meaningless facts." These are hardly the creative skills that spring to mind as empowering the emergence of civilization and culture.

Despite its title, *The Exceptional Brain* presents relatively little information relating talent to brain function. Neuropsychological test scores or the results of neurological examinations are provided in some cases but are not effectively related to brain function. Little attempt is made to answer the editors' original questions about the neurological substrate of exceptional abilities. The other shortcoming of the book is the restricted range of talents addressed. There is no discussion of painting, sculpture, theater, or dance, and science—by far the most prolific creative activity of the twentieth century—receives only 2½ pages of discussion.

Despite these limitations, *The Exceptional Brain* bravely breaks new ground in studying a neglected and important human activity. It is the most comprehensive account in the literature of the neuropsychological assessment of individuals with exceptional skills. Many of the chapters describe fascinating if often tragic individuals, and the quality of the writing is high throughout. The volume will be a valuable guide to readers interested in the neuropsychology of unusual abilities.

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Actual Minds, Possible Worlds, *by Jerome Bruner. Cambridge, Harvard University Press, 1986, 192 pp., $15.00; $7.95 (paper).*

In 1962, Jerome Bruner received a Distinguished Scientific Contribution award from the American Psychological Association for his "ground-breaking research on fundamental aspects of conceiving and thinking." In 1987, for outstanding achievements in human psychology, he was awarded the Balzan Prize, an equivalent in the humanities and social sciences to a Nobel Prize.

The year of his American Psychological Association award, Bruner published *On Knowing: Essays for the Left Hand* (1), a collection of "fugitive essays" reflecting "one of those mild crises so endemic to students of mind." They mark the beginning of his movement beyond the disciplinary constraints of psychology into the wider domains of literature and the arts. His new book, *Actual Minds, Possible Worlds,* a companion to the earlier one, shows us some of the signposts along his 25-year journey from distinction as a psychologist to his current prominence well beyond the boundaries of his home discipline. The essays assembled here express a general point of view on language and cognition that Bruner has been struggling to formulate over many years, but they are not an organized or systematic statement of his position.

The book's special contribution is Bruner's argument for the importance of narrative modes of thought. He begins by contrasting two modes of thought, "each providing distinctive ways of ordering experience, of constructing reality." These are the logical-scientific or paradigmatic and the narrative ways of thinking, the first exemplified by formal arguments and scientific explanations and the second by stories. Complementary but irreducible to each other, they involve different types of causality and different criteria of adequacy or goodness—truth for the first and verisimilitude for the second. To ignore either is to "fail to capture the rich diversity of thought." Narratives take as their topic the "vicissitudes of human intention," are open to various interpretations, and "initiate and guide a search for meanings among a spectrum of possible meanings." They succeed by "subjunctivizing reality," a mode for "trafficking in human possibilities rather than in settled certainties."

Proposing the study of great works of fiction, since they "come closest to revealing 'purely' the deep structure of the narrative mode," Bruner compares a short story by James Joyce with an ethnographic description and a reader's retelling of the story. Counting the number of linguistic transformations used that "subjunctivize" events (that is, open up their possible meanings), he finds that the ethnographic description has only half as many as the story, whereas the reader's retelling is remarkably similar to the original in both number and types of transformations. Bruner argues that the first comparison shows how narrative and paradigmatic discourses differ and the second shows that " 'great' storytelling, inevitably, is about compelling human plights that are 'accessible' to readers . . . set forth with sufficient subjunctivity to allow them to be rewritten by the reader" (p. 35).

The story of narratives, of stories and storytelling, is now an intellectual growth industry. Over the past 10 to 15 years, investigators and theorists in every branch of the human and social sciences, including psychoanalysis, have made the same discovery: telling stories is endemic in human cultures and serves important social and psychological functions. Despite the diversity and energy of narrative research, it is still marginal to the mainstream, positivist approach that dominates theory and research. Bruner's unequivocal stance on the importance of narrative modes of thought will strengthen the legitimacy of this wide-ranging effort. Nonetheless, for other students of narrative, what is most notable about Bruner's approach is its idiosyncrasy. It is neither related nor responsive to prominent directions of inquiry. Oddly, given his own work, he is inattentive to research on the functions of children's narratives for their learning how to speak and think. He is also silent about one of the central questions in theoretical and empirical work on narratives, namely, how to characterize their structure.

Other essays comment on education and developmental theory, thought and emotion, and the self and language. A somewhat ill-tempered afterword inveighs against Marxist and deconstructionist literary critics. Bruner has two heroes: Lev Vygotsky, the great Soviet psychologist, and Nelson Goodman, the U.S. philosopher. The former's theory of cognitive and linguistic development changed Bruner's approach from his earlier model of the "solo child mastering the world by representing it to himself on his own terms" to recognition that "most learning in most settings is a communal activity, a sharing of the culture" (p. 127). Goodman's constructivist argument that "world-making" is the primary human activity in our search for meaning is a recurrent theme and resource: "It is far more important, for appreciating the human condition, to understand the ways human beings construct their worlds . . . than it is to establish the ontological status of the products of these processes. For my central ontological conviction is that there is no 'aboriginal' reality against which one can compare a possible world in order to establish some form of correspondence between it and the real world" (p. 46).

This book is like a star turn, where a virtuoso performer takes a day off to talk informally about his enthusiasms and favorite texts. We come away from the performance with a sense of his personal style and way of thinking. For some readers, this may be sufficient. Others, responding to the book as an invitation—as a "subjunctive" account to be "rewritten"—can turn to the original sources and begin their own journeys into exciting areas of inquiry.

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NEUROPSYCHIATRY

Cerebral Dynamics, Laterality and Psychopathology: Proceedings of the Third International Symposium on Cerebral Dynamics, Laterality and Psychopathology, *edited by Ryo Takahashi, Pierre Flor-Henry, John Gruzelier, and Shin-Ichi Niwa. Amsterdam, Elsevier, 1987, 572 pp., Dfl 360.00.*

This volume contains the proceedings of a symposium held in Hakone, Japan, in October 1986. The volume demonstrates that more than two decades after Flor-Henry's seminal study relating a left epileptic focus in temporal lobe epilepsy and schizophrenia-like psychosis, interest in the relationship between psychopathology and laterality continues unabated. However, as with neurochemical approaches to psychiatry, which have moved past the one-amine, one-disease phase, so too laterality research has outgrown its phrenological roots and no longer assigns all psychiatric illnesses to either the left or the right hemisphere. Interest has shifted toward an understanding of the integration and disintegration of functions between left and right, anterior and posterior, and cortical and subcortical brain structures.

Because the 69 papers in this volume use such a wide range of methodologies (electrophysiology, neuropsychology, neurochemistry, brain imaging, etc.), any attempt to highlight a particular set of papers for discussion will lead to idiosyncratic choices, reflecting the limits of my knowledge and interests. Be that as it may, certain contributions stand out in my mind. First, there is Richard Davidson's survey of a series of experiments with neonates, infants, and adults. The results of these experiments support the overall hypothesis that emotions associated with approach behavior induce asymmetries favoring left frontal activity and emotions involving withdrawal involve asymmetries favoring right frontal activity. A second series of experiments demonstrates that individual differences in frontal activation are associated with affective styles and psychopathology. For example, depressed subjects show less frontal activity at resting baseline than nondepressed subjects. Aside from the internal consistency of such findings, they have the additional advantage of being consistent with our understanding of cognitive asymmetries of function. Approach might be expected to require the planned, sequential type of reasoning associated with left hemispheric function. A call for retreat might best be made after a global synthesis, favored by the right hemisphere. These findings also provide a theoretical framework from which to examine asymmetries in the distribution of neurochemicals (such as dopamine, norepinephrine, serotonin, and opioids) that might be expected to mediate approach and withdrawal behaviors. In this regard the report by Reynolds and Czudek of their ability to replicate the finding of greater left-sided dopamine in the amygdala of schizophrenic subjects than in the amygdala of normal subjects may be of interest.

A different but equally elegant series of experiments is described by Paul Green, who used an experimental paradigm that examines story comprehension when auditory input is delivered to each ear separately or to both ears simultaneously. He demonstrates in a wide range of disorders (including schizophrenia and affective states) that individuals often reveal strikingly less comprehension with binaural presentation than with presentation to the superior ear alone. In addition, the decrement on binaural presentation can be reduced by placing an ear plug in the ear with poorer comprehension. One's interest in such findings is piqued by well-documented reports of schizophrenic individuals who have experienced reductions in auditory hallucinations with a well-placed earplug. In a larger perspective, such findings are strong support for Green's view that it is not a deficit in interhemispheric transmission but, rather, interference due to such transmission that might underlie certain psychopathological symptoms. In addition to the chapters just discussed, there are many other intriguing contributions that warrant perusal of this volume by students of biological psychiatry.

Since plans are now being made for a Fourth International Symposium, which will no doubt produce another volume, it might be in order to offer specific criticisms or recommendations. Symposium proceedings tend to be difficult to read. Aside from their archival value, they usually function as reference volumes, approached by readers interested in a few specific chapters. Only the truly devoted researcher or most scrupulous reviewer might be expected to read them cover to cover. This volume is no exception. Despite comprehensive introductory chapters by both Flor-Henry and Gruzelier, moving between the separate chapters often produces a disjointed effect. This might be reduced by having selected contributors assigned to provide reviews that would facilitate the reader's ability to integrate the specific, often recent findings noted in the majority of chapters. In addition, since strong and often conflicting viewpoints and personalities abound, a series of debate formats might sharpen differences. Would Peter Jennings agree to moderate?

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The Psychiatric Treatment of Alzheimer's Disease: Report 125, *by the Group for the Advancement of Psychiatry Committee on Aging. New York, Brunner/Mazel, 1988, 148 pp., $20.00.*

One of the challenges of being a clinician who works with older adults is overcoming the pervasive attitude that there is no treatment for Alzheimer's disease. Many people, including physicians, have a general feeling that the diagnosis of dementia of the Alzheimer type is an end in itself rather than the start of specific treatment. There is no disputing the fact that, at the present time, there is no curative treatment for Alzheimer's disease. However, the attitude that less definitive interventions in Alzheimer's disease are somehow lacking in value is curious indeed. Much of medicine is devoted to the care of individuals with incurable illness. For some reason, victims of Alzheimer's disease and their families have been slow to come under this benevolent paradigm of medical care. The notion that dementia has no treatment has had the unfortunate effect of isolating the affected individuals and their families, depriving them of potentially valuable aid in coping with the disease.

The Psychiatric Treatment of Alzheimer's Disease, written by the Committee on Aging of the Group for the Advancement of Psychiatry (GAP), presents compelling evidence that there is much that can be done for victims of this disorder. The text flows from the twin premises that Alzheimer's disease is not synonymous with normal aging and that the major clinical problems confronted in Alzheimer's disease are behavioral and psychosocial in nature. Emphasis throughout is placed on the relief of excess disability states produced by unrecognized and untreated coexisting disorders, such as depression and other physical illnesses. The importance of approaching Alzheimer's disease as a disorder that has recognizable stages with problems unique to each stage is also appropriately given weight.

This relatively brief text has a number of features that make it particularly rewarding to read. First, the chapters are either all written by a single author or edited to give this appearance, thus avoiding the unevenness of multiauthored texts. The well-organized chapters include a brief overview of Alzheimer's disease, "Clinicopathologic Correlations," "Diagnosis," "Treatment," and "Case Examples." The case reports represent one of the real strengths of the book. Ten typical case studies are presented, each accompanied by a brief but insightful discussion containing valuable clinical wisdom. The cases convincingly demonstrate the myriad ways a physician can treat this "untreatable" disorder. An appendix includes several of the most widely used instruments for rating various aspects of the course of the disorder.

Problems with the book are relatively minor. The chapter on diagnosis includes the erroneous statement that rigidity and myoclonus are "not infrequently encountered in the early stages of Alzheimer's disease" (p. 33) when in fact these features are typically seen late in the course of the disorder. The statement of purpose misidentifies the book as having been formulated by the Committee on Public Education (p. v). Finally, the Geriatric Depression Scale (1) is the only depression scale included in the appendix, despite the fact that data on the validity of this self-report scale in Alzheimer's disease are lacking.

This book is appropriate for a wide audience, extending from medical students and residents to the practicing physician. The authors of this fine volume may have unnecessarily limited their audience by entitling the volume *The Psychiatric Treatment of Alzheimer's Disease.* Much of this text will be of interest to any physician interested in the challenge of treating patients with this disorder.

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WILLIAM J. BURKE, M.D.
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Facial Dyskinesias: Advances in Neurology, vol. 49, *edited by Joseph Jankovic and Eduardo Tolosa. New York, Raven Press, 1987, 560 pp., $102.00.*

The most distinctive part of the body of a primate, especially that of homo sapiens, is the face. Robert Browning, in *A Likeness,* alluded to the importance of the face when he wrote,

> A face to lose youth for, to occupy age
> With the dream of, meet death with.

The human face has 80 different muscles at its disposal to express various kinds of emotions. Unfortunately, these muscles can also be struck by different types of maladies, resulting in a plethora of movement disorders called facial dyskinesias.

This book, edited by Dr. Jankovic of Houston, Texas, and Dr. Tolosa of Barcelona, Spain, includes such conditions as Meige's syndrome, other causes of blepharospasm, spasmodic torticollis, hemifacial spasm, idiopathic oral-facial dyskinesia, tardive dyskinesia, palatal myoclonus, spasmodic dysphonia, and nocturnal bruxism. There are 56 contributors, mainly neurologists from the United States, Spain, and the United Kingdom.

Some chapters are reviews (e.g., "Local Side Effects of Botulinum Toxin Injections" by Patrinely et al.), and some are presentations of the authors' own data (e.g., "Acute Pharmacologic Tests in Cranial Dystonia" by Gimenez-Roldan et al.). A few chapters (e.g., "Brain Stem Pathology in Cranial Dystonia" by Zweig and Hedreen) deal with basic science aspects of the disorders.

The particularly well-written chapters include "Physiology of Normal and Abnormal Blinking" by Karson, "Blepharospasm: A Form of Focal Dystonia" by Fahn, "Tardive Dystonia" by Burke and Kang, and "Palatal Myoclonus and Facial Involvement in Other Types of Myoclonus" by Dubinsky and Hallett. The strongest section of the book is on blepharospasm. There are at least six chapters devoted primarily to clinical aspects and pathophysiology of blepharospasm and four to its treatment (pharmacological as well as surgical). The pharmacology of the botulinum toxin is also covered extensively in the section on management.

This monograph is an excellent reference book on facial dyskinesias. Some concepts in the book, however, are rather unconventional. For example, tremors are included in dyskinesias. Although the term "dyskinesia" is admittedly very broad and can include any type of abnormal movements, traditionally tremors are excluded from the definition of dyskinesia.

The book seems to be targeted more to neurologists than to psychiatrists—for example, the management of blepharospasm is covered extensively, but the treatment section of the book does not include any chapter on the management of tardive dyskinesia. Nonetheless, the book includes detailed discussions of a number of facial dyskinesias and will be useful for neurologists as well as for researchers in movement disorders.

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Chronic Pain, *edited by Randal D. France, M.D., and K. Ranga Rama Krishnan, M.D. Washington, D.C., American Psychiatric Press, 1988, 546 pp., $32.00.*

There are few arenas in clinical medicine better suited for psychiatrists to demonstrate their expertise in formulating and implementing integrated medical-psychiatric treatment plans than chronic pain programs. The phenomenon of chronic pain and its behavioral consequences require assessment of multiple systems, including the neuroanatomical, neurophysiological, psychiatric, family, behavioral, sociological, and pharmacological. Although many other disciplines make essential contributions to the assessment and treatment of patients with chronic pain, only the psychiatrist possesses the necessary skills and background to fully integrate these multiple factors into a comprehensive understanding of the patients' symptoms and behavior. In this volume, the editors provide an overview of this complex diagnostic and treatment process. Basic neurophysiological and neurochemical aspects of chronic pain are considered as well as how the contribution of personality variables, concurrent psychiatric disorders, and operantly conditioned behaviors contribute to the phenomenon of chronic pain.

With one exception, all of the authors were originally faculty and staff from the pain treatment program at Duke University Medical Center, Durham, N.C. Psychiatry, behavioral psychology, physical therapy, neurosurgery, and nursing are all represented. The text begins with introductory chapters presenting a systems approach to assessing chronic pain, and then basic concepts in the neurophysiology and neurochemistry of chronic pain are discussed. The basic science chapters are succinct and generally adequate for a primarily clinical text but dated—most of the more recent references are from 1984; a few are from 1985 and 1986. For a field as rapidly expanding as the neurochemistry of pain, one must assume that there was some delay in publication.

The book's strongest suits are the chapters that address the clinical management of chronic pain, particularly those on the use of adjunctive psychotropics and behavioral assessment and behavioral therapy. Of particular note are the contributions of the editors, France and Krishnan, and the behavioral psychology chapters either authored or co-authored by Francis J. Keefe. These chapters on behavioral approaches are lucid and will be helpful to psychiatrists interested in the application of operant treatment paradigms for patients with chronic pain.

The general organization of the text could have been improved—for example, there are four separate chapters on behavioral assessment; if they had been grouped together and integrated they would make an excellent monograph in themselves. The scatter of behavioral and pharmacological chapters clearly demonstrates that the editors favor a multidisciplinary approach, but we need to know how these treatments can be practically integrated and implemented in the clinical setting. Likewise, the time-intensive multidisciplinary approach is inevitably quite expensive, but the issue of cost effectiveness is not addressed, and long-term outcome data are not presented or discussed. Finally, with the exception of cancer pain, specific pain syndromes such as headache are cryptically covered. For example, the critical distinction between cluster migraines and sphenopalatine neuralgia (also referred to as cluster headache) is not made. There is a tendency to take a rather generic approach to pain management, especially in the chapters on behavioral assessment and treatment.

The strengths of this text are its emphasis on comprehensive behavioral assessment, attention to concurrent psychiatric morbidity, and superb reviews of the use of adjunctive psychotropics in the clinical management of chronic pain. In this respect the book provides a useful and important guide to an emerging psychiatric subspecialty that is crystallizing as an area in clinical medicine in which psychiatry can be both visible and viable.

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Soft Neurological Signs, *edited by David E. Tupper, Ph.D. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich), 1987, 388 pp., $37.50.*

For many physicians, even neurologists and psychiatrists, the subject of soft signs is something distantly remembered from medical school days. If asked, one recalls, perhaps with some embarrassment, that there are an awful lot of soft signs—too many to remember, in fact—but they probably have something to do with brain damage or hyperactivity or learning disorders. It turns out that one needs to know quite a bit about soft signs before it is possible to say anything much more cogent than this. Indeed, this book makes a convincing argument that a little knowledge about soft signs might indeed be intellectually dangerous.

Medicine in general and psychiatry in particular are bedeviled with poorly defined concepts (such as soft, or equivocal, neurological signs) that make sense in different ways to different practitioners. Dr. Tupper does not pretend to eliminate all ambiguity. Rather, he presents soft signs as one of those phenomena which are "intriguing not because they are clearly valid and useful scientifically, but because they defy our easy explanation and intuition and tell us something further about our own thinking and our approach to the problem" (p. 1). This is a thoughtful book that, although nominally aimed at both the clinician and the researcher, is probably going to be of more immediate use to the latter.

Soft Neurological Signs is organized into three sections: Assessment, Research, and Meaning. There is also an appendix of soft sign examinations. If one simply wanted to know whether soft signs have clinical correlates, the Research section might be the best one to turn to. This is where the question of whether soft signs are convincingly associated with any clinical syndrome is approached most directly.

Several of the authors in this section rely on information gleaned from the huge Collaborative Perinatal Project of the National Institutes of Health, which was started in 1959. The study was conducted in 15 medical centers and enrolled 50,000 women and their offspring. All manner of data touching on pregnancy history, pre- and perinatal events, postmortem examinations, and later childhood functioning have been collected.

Abraham Towbin, in "Neuropathologic Correlates," discusses the variety of traumatic events that can happen to the fetus and infant and their long-term neurological consequences. He suggests that much of the information on pathology that emerged from the Collaborative Perinatal Project has yet to filter down to the clinician. For example, he points out that the popular conception that forceps delivery is an important cause of brain injury is erroneous.

In another chapter, Paul L. Nichols attempts to correlate soft signs with the "minimal brain dysfunction" syndrome in a group of 7-year-old children from the Collaborative Perinatal Project. (Children with cerebral palsy and mental retardation were excluded from this study group.) Again, the shibboleth fails: soft signs were not found to be clearly related to minimal brain dysfunction. Nichols found that although the various soft signs assessed correlated well with each other, they correlated poorly with measures of hyperactivity or learning disorders, traditional components of the minimal brain dysfunction syndrome.

Other chapters in this section examine the relationship of soft signs to more discrete syndromes: learning disabilities, hyperactivity, choreiform movements, and low birth weight. Each chapter is written by an investigator who is active in soft sign research. Each combines some degree of historical review with a presentation of the author's own data and avoids sweeping conclusions. Not surprisingly, all of the authors note the lack of uniformity in definitions and measures of soft signs across different studies.

If one either is prepared to jump into deep waters straightaway or has been forced, by reading the Research section, into thinking about the complexity of determining what should be called a soft sign and how to measure it, one moves back to the Assessment section. Dr. Tupper kicks off gently enough with an overview of the issues in soft signs. William Yule and Eric Taylor continue with "Classification of Soft Signs," which is largely based on the famous Isle of Wight study, an epidemiologic survey that included about 1,000 children in age groups ranging from 5 to 15 years. They offer a preliminary classification of soft signs into three groups: signs of developmental delay, signs due to both neurological and other factors, and slight abnormalities that are difficult to detect. In the next chapter, Perry C. Goldstein and Dr. Tupper launch into a detailed discussion of reliability and validity that could easily be the synopsis for an entire semester's course. In spite of the complexity of the subject, this is a very readable chapter. Concepts are presented clearly and are illustrated directly from soft sign research. One then proceeds through "The Assessment of Nonfocal Signs in Children" to "Developmental Motor Signs," another weight chapter, which includes a number of normative tables fo motor soft signs and can, to some extent, be used in conjunction with the assessment batteries in the appendix.

Given that some would find that a definition of soft sign should not include EEG findings, it is not surprising tha there is only one chapter dealing specifically with electroencephalography. This chapter, although brief, is excellent Normal EEG findings are presented for developmental stage from those of premature infants to those of the elderly. Sof abnormalities are delineated against this developmenta background.

In summary, if one is strictly a clinician, *Soft Neurologica Signs* is an excellent book to have if you are going to hav any book on such things. (Until soft signs are better understood, it still may be possible to ignore them.) Although i covers a very difficult subject, it does not have any poorl written chapters. Research on soft signs clearly must tak into account a number of thorny methodological issues. Dr Tupper seems to really want someone to do something abou the current difficulty with conceptualizing soft signs and ha done his best to provide the necessary tools for the researcher. With an understanding of the failures of previou studies plus what is provided in this book—the instrument in the appendix, the normative data in the Assessment section, and the generous referencing throughout—designing methodologically sound study becomes much more possible

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Advancing Frontiers in Alzheimer's Disease Research, *edite by George G. Glenner, M.D., and Richard J. Wurtman M.D. Austin, University of Texas Press, 1987, 262 pp. $22.50.*

This volume is based on a symposium on Alzheimer's disease research held in June 1986 by the Mind Science Foundation. It contains reports of new, creative research approaches and raises many hypothetical questions abou possible etiologies for Alzheimer's disease, such as phospholipid defects and aberrant choline metabolism, neurona membranes, vulnerability to excitotoxin-mediated cellula damage in relation to synaptic plasticity, and prion-induce neuronal damage. The volume also contains comprehensiv reviews of neuronal biochemistry and neurotransmitter systems in Alzheimer's disease, animal models of Alzheimer' phenomena, Down's syndrome as related to Alzheimer's disease, clinical diagnostic issues, and newer neuroimaging an cognitive techniques and cognitive tests as applied to Alzheimer's disease.

The topics covered in this volume are generally though provoking, insightful, and of value to both researchers an clinicians interested in Alzheimer's disease. It seems unfortunate that the symposium's discussions were not included i the volume, since insightful research ideas and additiona evidence are often put forward in discussion sessions. Nonetheless, this volume would make a useful contribution i expanding the reader's knowledge and creative thinkin about Alzheimer's disease.

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ALCOHOLISM

Recent Developments in Alcoholism, vol. 6, *edited by Marc Galanter. New York, Plenum, 1988, 411 pp., $65.00.*

The four sections of this volume survey the topics of substance abuse and posttraumatic stress disorder (PTSD), the development of employee assistance programs, consequences of alcohol use in women, and risk markers for alcoholism. Most chapters use the somewhat ponderous literature review format. They are generally written conscientiously, and there is something to be learned in each chapter.

The text's most successful section is about the workplace. It comprehensively presents the development of workplace interventions regarding alcoholism, starting with background epidemiology. It reviews weaknesses in assessment of alcohol abuse and sequelae and considers the relationships between job stresses and drinking. An especially interesting chapter traces the recent evolution of scientific thinking and public policy regarding alcoholism. Chapters describe the administration of various approaches of employee assistance programs to identification and treatment from both the employers' and the workers' points of view as well as reentry into the workplace, including limited consideration of maintenance strategies. Overall, the section is accessible and reads well.

The section on consequences of alcohol use and abuse in women is the most disappointing because of the limited vision of the editor. This section has the greatest potential to synthesize what is known in basic clinical and social sciences regarding alcoholism in an identified population. The limited scope is especially glaring in proximity to a well-developed section on veterans. The selection of endocrinology as the vehicle for understanding women reflects the basic sexism in medicine that leaves women alienated from their medical caretakers. A more appropriate title for this section would have been "Consequences of Alcohol Abuse Unique to Women's Organs." This very basic editorial problem does great disservice to the authors of the four very thoughtful and interesting chapters. They have tried hard to explain endocrinology, fetal development, pharmacodynamics, absorption and metabolism, and liver disease for the general psychiatrist. The chapters are somewhat dense but readable, and the topics chosen are intriguing. Devoting a chapter to examining moderate alcohol use is innovative. It adds depth to a field where clear-cut abuse and end-stage problems are usually the only topics of investigation. The chapter on sex differences in alcohol metabolism and hepatotoxicity is very interesting, but placing it in a specially designed section on women reflects the sexism already noted.

The section on patients with alcoholism and PTSD examines this dually diagnosed group from all angles. The section is appropriately expanded to include polysubstance abuse. The relationship among combat exposure, psychiatric symptoms, and substance abuse symptoms is explored. Current data on brain anatomy, neurotransmitter systems, learned helplessness, and the effect of withdrawal states are brought together. Coping and defending styles are dynamically dealt with. The final chapter on PTSD in veterans of World War II and Korea remembers these often overlooked groups. Although each chapter is interesting on its own, what makes the section exceptional is its success in pulling together so many fields of psychiatry.

Within its admittedly limited scope, the section on risk markers for alcoholism attempts to explore advances in a variety of areas, including family histories, twin studies, and frequency of coexisting psychopathology, brain evoked potentials, molecular genetics, blood tests, and alcohol and acetaldehyde metabolism. There is also a review of discriminant function analysis, the closest thing to direct clinical application of risk marker research. This is a method of combining and evaluating various data in an attempt to diagnose alcoholism, risk for alcoholism, or progression of alcoholism. The authors of these chapters conscientiously try to provide sufficient orientation and background before immersing the reader in topics unfamiliar to the general psychiatrist. The writing tends to be dense as the authors attempt to describe each field in detail. The uninitiated reader will find this section slow going but will get a well-rounded introduction to an exciting area of research.

The problem with this volume is in the editing. It is neither an introductory text nor a comprehensive text. The sections are uneven in the thoroughness with which they examine their topics, and there is no attempt to tie them together. The first three sections seem to have thematic potential. They review recent efforts to understand and treat the different faces of alcoholism in different subpopulations in our society: veterans, workers, and women. This text could begin to assemble a framework for understanding alcoholism in our society but, instead, persists in chasing details. The section on risk markers seems misplaced in this volume. Sections on alcoholism in minority groups and children, on dual diagnosis, and on the changing attitudes of our government and society toward alcoholism would have been more consistent.

The *Recent Developments in Alcoholism* series is not meant to be general textbooks on alcoholism or to be the first additions to a young alcohologist's library. In fact, there may be no basic textbook about alcoholism and addictions for psychiatric and other health care practitioners, a problem that the sponsors of this series might do well to address.

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Is Alcoholism Hereditary? 2nd ed., *by Donald W. Goodwin, M.D. New York, Ballantine Books, 1988, 259 pp., $7.95 (paper).*

This is a gem of a book. The author covers a mélange of topics related to alcoholism, its causes, and its treatment. Successive chapters teach the reader about the drug alcohol and the problem of alcoholism, document the severity of the difficulties associated with this disorder, educate the reader about approaches for establishing a genetic component of a problem, and offer details about the studies of the importance of genetic factors in alcoholism itself.

The outstanding characteristic of this book, however, is the style of writing. Taking an easygoing and chatty approach, the author is at once informative and pragmatic. The latter is exemplified in the series of questions and mythical polemical discussions that pepper the pages as well as in the final section of the text, which succinctly summarizes the major issues. The horrors inherent in the life of an alcoholic are handled with understanding and respect, as are the allusions to Alcoholics Anonymous, various treatment approaches, and the wide array of research going on in this field.

Assimilating this information is made not only bearable but enjoyable through the skillful incorporation of quotations, anecdotes, and references to English literature. Many of these are based on a series of earlier writings on the "muse and the martini" published by Dr. Goodwin in various journals over the years. I especially enjoyed the anecdote quoted from Jack London's *John Barleycorn* on page 69, the frequently tongue-in-cheek brief quotations that start many of the chapters, and the incorporation of specific quotes from O'Neill's *Long Day's Journey Into Night.*

Despite this literary approach, much pragmatic information is offered. The discussion of studies of the genetics of alcoholism skillfully translates research jargon and relatively complex statistics into useful information. Similar comments can be made about the author's treatment of the pharmacology of alcohol, his highly pragmatic discussion of the definition of alcoholism, and his thoughts on its treatment.

Of course, it would be impossible for anyone to write a book and have a reader who works in that field agree with everything that is said. The possible importance of an actual diagnosis of familial alcoholism is perhaps a bit overplayed, an understandable consequence of Dr. Goodwin's work in that area, and this is not a book for individuals who desire detailed discussions or who want easy access to a large number of references from the scientific literature. Neither of these would be consistent with the overall goal of reaching out to a general audience in an attempt to both teach and entertain.

All in all, I give this text high praise. In this age of self-help books, I tend to tune out as I walk by the psychology section of my favorite bookstore. However, I overcame my prejudice against popular psychology in science long enough to pick up this delightful book. My effort was amply repaid.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Anabolic Androgenic Steroids and Suicide

SIR: The medical and psychiatric complications associated with the emerging epidemic of anabolic androgenic steroid abuse are a major concern for physicians (1). The intent of this letter is to call attention to suicide as another possible complication and to suggest that medically supervised detoxification may be preventive.

Although substance abuse in general is a known risk factor for suicide (2), to our knowledge no controlled studies have addressed specifically an association between anabolic androgenic steroid abuse and suicidal ideation. Nevertheless, recent case reports in both the professional literature (3, 4) and the press indicate that some steroid users become depressed and suicidal. Most tragically, the newspapers have recently reported two cases in which steroid users committed suicide. Whether these individuals were predisposed to suicide before their steroid use or whether they developed suicidal depressions because of their steroid use is unclear. In at least one other case (3), however, there was neither a past personal history nor a family history of depression or suicidal tendencies that would have contributed to the risk of suicide.

A recent study (5) suggested that steroid users are most vulnerable to major depressive episodes during the first 3 months following discontinuation of steroid use. Therefore, chronic steroid users should seek professional supervision before discontinuing steroids, because depression and the potential for suicide are especially likely during this withdrawal period. Addicted steroid users (3, 4) may possibly benefit from a tapering course of medically prescribed steroids, because abrupt discontinuation of steroids may precipitate severe depression and suicide. It must be stressed, however, that the detoxification of anabolic steroid abusers is an unstudied area, and the prescription of an abused substance to a substance abuser can be problematic unless there is close supervision. We also recommend caution in using clonidine for steroid detoxification as described by Tennant et al. (4), because clonidine itself has been associated with depression, and such treatment is based on the results in only one case. Antidepressant medication, which has shown promise during cocaine withdrawal, deserves a study trial in the treatment of anabolic steroid withdrawal.

In conclusion, psychiatrists need to be alerted that depressed athletes and bodybuilders may be abusing steroids, which could possibly increase their risk of suicide. Patients need to be questioned carefully and nonjudgmentally about their possible use of steroids, since they may be reluctant otherwise to volunteer this information. Urine testing, when available, can be helpful in detecting hidden steroid use. Additional studies are needed both to assess further the psychoactive effects of steroids, including suicidal tendencies, and to determine the optimal treatment for steroid abuse. Finally, psychiatrists need to be knowledgeable about the medical and psychiatric presentations of steroid use (1, 3–5) and to have greater clinical access to urine testing for steroids, because early detection and treatment of steroid abuse could mean the difference between life and death.

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Manic Syndrome After Discontinuation of Methyldopa

SIR: Manic syndromes can have numerous organic causes. In the review by Krauthammer and Klerman (1) and the more recent review by Stasiek and Zetin (2), drugs, infection, neoplasm, epilepsy, and metabolic disturbance were most often responsible for secondary mania, and a recent report (3) revealed two cases of zidovudine-induced manic syndrome. We report a case of manic syndrome following discontinuation of 12-year methyldopa therapy.

Mr. A, a 62-year-old hypertensive, Caucasian man, came to our clinic 4 weeks after his medication had been switched from methyldopa to nifedipine because he had reached the maximum methyldopa dose and had been complaining of lethargy. His other medications, triamterene, potassium chloride, and clonidine, were unchanged during this period. Two weeks before admission he noted the abrupt onset of elated mood, rapid intrusive thoughts, loud, pressured speech, and decreased appetite and sleep requirements. He contemplated starting several unusual businesses and while driving would pull off the road to write down ideas. He came to our clinic on his way to the Orient to visit a woman whom he had not contacted in many years. He was hospitalized because of mania.

Mr. A had never suffered similar symptoms and had no family history of mood disorder. He noted now that he had felt "sluggish in the morning" during methyldopa treatment, but denied anhedonia, neurovegetative symptoms, anergia, or suicidal ideation. He had never sought help from a psychiatrist.

Results of a neurologic examination, head CT scan, thyroid function tests, vitamin B12 and folate levels, EEG, electrolyte levels, liver function tests, CBC, ESR, antinuclear antibodies, and a urine drug screen were all normal, as were the results of a cognitive examination. His blood pressure was elevated in the hospital, but it never reached the malignant range. Mr. A responded gradually within a fortnight to treatment with lithium and haloperidol.

Methyldopa is associated with depression in some patients (4). It is thought to exert its hypotensive effects within the CNS (by conversion to α-methylnorepinephrine, a powerful α_2 receptor agonist) (5), and we postulate that Mr. A's norepinephrine receptor sensitivity was altered by methyldopa therapy. After discontinuation, then, there was a "secondary mania." Just as only certain patients develop depression from methyldopa, our patient may have had a pharmacologic vulnerability to developing mania after discontinuing the drug. It is difficult to ignore the temporal relationship between stopping the methyldopa and this first manic syndrome. It is, however, possible that this represented an epiphenomenon and that the patient suffered late onset of bipolar disorder.

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Mania Triggered by a Steroid Nasal Spray in a Patient With Stable Bipolar Disorder

SIR: Mania can occur in Cushing's syndrome (1) and has regressed after ablation of the causative tumor (2); it can also be an effect of exogenous steroids (3). It is not known how much cortisolemia is required to produce mania or whether patients with bipolar disorder are at increased risk. We report the case of a patient with bipolar disorder in remission in whom acute mania was triggered by a steroid nasal spray. Serum cortisol was within normal limits.

Ms. A, a 28-year-old white woman, had had her first manic episode at age 20. Since the age of 25 she had had six hospitalizations for mania. The characteristic pattern was a 4- to 8-week evolution from hypomania (often associated with illicit drug use and noncompliance with her lithium regimen) to mania with psychosis, followed by a return to baseline functioning after 4–5 weeks of hospitalization, antipsychotics, and lithium.

For the year preceding the steroid episode, Ms. A had been a model patient, with therapeutic blood levels of lithium, convincing and family-confirmed denials of drug abuse, gainful employment, and education plans; she was taking an active and intelligent role in the management of her own illness. Then, one day she presented with chills and postnasal drip; radiography revealed her frontal sinuses to be either poorly developed or fluid-filled. She was given a prescription for erythromycin, 250 mg q.i.d. by mouth, and one puff of beclomethasone nasal spray in each nostril as needed.

Five days later, Ms. A's companion brought her to the emergency room because of the abrupt onset of mania characterized by insomnia, belligerence, and irrational speech. On admission she was barefoot and agitated, wearing soiled clothes, and bruised from skirmishes with the ambulance staff. She verbalized flights of ideas concerning babies, nuclear war, Mother Nature, and Arizona going into the ocean to cleanse its wounds.

She was admitted to the psychiatric service in restraints. Her initial medications included clonazepam, 1 mg t.i.d. by mouth; 1 mg of lorazepam alternating with 5 mg of fluphenazine orally or intramuscularly each hour as needed; and 1–2 mg of lorazepam for sleep. Beclomethasone was discontinued, erythromycin was continued for 20 days, and lithium was continued at the previous oral doses of 600 mg every morning and 900 mg at bedtime.

Ms. A's serum lithium level was 0.7 meq/liter 20 hours after admission (therapeutic range=0.7–1.2 meq/liter) and her serum cortisol level was 17 μg/dl 2 mornings after admission (normal morning level=17–22 μg/dl). A urine drug screen produced negative results.

Carbamazepine and thiothixene were added and then tapered, and the clonazepam was tapered. The patient was discharged from the hospital after 2½ weeks. She was subsequently followed up for 9 months and returned to the same level of functioning and stability as before this episode.

Although erythromycin may produce mild psychiatric symptoms (4), Ms. A's abrupt onset of mania coincident with inhaler use, her laboratory-confirmed abstinence from drugs of abuse, her compliance with her lithium treatment, and the rapid evolution of the manic episode suggest that beclomethasone may trigger mania in a patient whose bipolar disorder is in remission. We are unaware of data suggesting increased susceptibility of bipolar patients to steroid-induced mania; however, females may be more susceptible than males (5).

The relationship between steroids and bipolar disorder merits further inquiry. This letter may stimulate other clinicians to report similar interactions.

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Family Histories of Alcoholism in Depressed Patients: DST and REM Latency Findings

SIR: While the coexistence of depression and alcoholism is well-known (1), few studies have examined the relationship between the results of the dexamethasone suppression test (DST) in depressed patients and their family histories of alcoholism. One study (2) showed that the morbid risk for treated alcoholism in the families of depressed patients who suppressed cortisol production following dexamethasone was more than two times greater than the risk for nonsuppressors. The relationship between family history of alcoholism and REM sleep latency is less well-known.

To further investigate DST results and measures of REM sleep latency in depressed patients with respect to family history of alcoholism, we studied 20 hospitalized patients who met the Research Diagnostic Criteria (RDC) for probable or definite major depressive disorder with endogenous features. All patients obtained a score of 20 or more on the Hamilton Rating Scale for Depression and were medically healthy and drug free. None had a history of alcoholism.

The patients were interviewed with the Schedule for Affective Disorders and Schizophrenia (SADS) and the Hamilton scale. The SADS was then used to derive RDC diagnoses. Family histories of alcoholism were obtained by independent interviews of each patient and two first-degree family members, according to the guidelines of the Family History Research Diagnostic Criteria (FH-RDC) (3). DSTs were then performed. Blood was drawn from patients to determine plasma cortisol levels at 8:00 a.m., 4:00 p.m., and 11:00 p.m. on the day of and the day following a 1-mg dose of dexamethasone at 11:00 p.m. Samples were analyzed by investigators blind to the subjects' diagnoses and family histories by means of a radioimmunoassay procedure described elsewhere (4). The patients underwent one night of polysomnography; REM sleep latency was determined by computing the elapsed time between sleep onset and the first epoch of REM sleep. DST and REM sleep data were obtained only from the depressed patients, not from family members.

Morbid risk for alcoholism was calculated according to the Weinberg shorter method (5). The ages of risk were 15–40 years, inclusive. One outlier in our sample who had extremely high morbid risk and cortisol values was excluded from the data analyses.

Results showed that there was no significant relationship between morbid risk for alcoholism and any pre- or postdexamethasone cortisol value. Pearson correlation coefficients for morbid risk and postdexamethasone cortisol levels obtained at 8:00 a.m., 4:00 p.m., and 11:00 p.m. were −0.17, −0.06, and −0.08, respectively. A positive, nonsignificant correlation ($r=0.28$) was found between morbid risk for alcoholism and REM sleep latency. There were significant negative correlations between REM sleep latency and postdexamethasone cortisol levels at 4:00 p.m. and 11:00 p.m. ($r=-0.48$, $p<0.03$, and $r=-0.62$, $p<0.01$, respectively).

When patients were grouped as DST suppressors (i.e., having a plasma cortisol concentration of <5 μg/dl) and nonsuppressors (>5 μg/dl), no significant difference was found in morbid risk for alcoholism and DST values at 8:00 a.m., 4:00 p.m., 11:00 p.m., and all times combined. Similarly, when patients were grouped by REM sleep latency values, there were no significant differences in morbid risk between those with short (≤60 minutes) and those with normal (>60 minutes) REM latency. No significant findings were obtained when analyses were repeated using only data from those relatives who had been treated for alcoholism.

The data presented here suggest that neither pre- nor postdexamethasone plasma cortisol levels nor REM sleep latency is associated with morbid risk for alcoholism in family members of depressed probands. Therefore, the well-documented familial relationship between affective disorder and alcoholism is not found to be marked by response to the DST. These findings may differ from those of Zimmerman et al. (2) because the present study used a different proband group (i.e., only subjects with diagnoses of major depressive disorder with endogenous features) and based FH-RDC diagnoses on three family members' reports rather than on probands' reports alone.

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DSM-III-R Definition of Mental Disorder

SIR: While acknowledging the difficulty in defining a mental disorder, *DSM-III-R* attempts to provide such a definition. However, from an analysis of the terms used, it appears that the definition does not have much to say.

The definition begins with the sentence, "Each of the mental disorders is conceptualized as a clinically significant behavioral or psychological syndrome or pattern . . . ." (p. xxii). There is no further specification of what is clinically significant. Since the most significant factor in a clinical context is the distinction between a disorder and nondisorder, the term "clinically significant" could perhaps mean the presence of a mental disorder. Further confirmation for such an assumption is found in a subsequent sentence that reads, "Whatever its original cause, it must currently be considered a manifestation of a behavioral, psychological, or biological dysfunction in the person." While it is conceded that a dysfunction is not necessarily synonymous with a disorder, when this sentence is read in conjunction with the earlier sentence, it appears that a dysfunction which is also causing clinically significant manifestations cannot be different from a disorder. So, the definition requires one to make an initial judgment about whether the "behavioral or psychological syndrome" is a mental disorder or not.

The rest of the definition provides certain inclusion criteria that must necessarily be present for the diagnosis of a mental disorder. Can these criteria, then, provide some objectivity to the definition by influencing the clinician's initial judgment about the presence or absence of a mental disorder? Apparently not, since the criteria include terms such as "important areas of functioning" and "important loss of freedom" without providing specifications for what is important—and important for whom (the patient, society, or the clinician?). The ambiguity of the terms leaves sufficient leeway for the clinician to ascribe to them whatever meaning suits his or her initial judgment.

The last sentence of the definition excludes "deviant behavior" and "conflicts . . . between the individual and society" from consideration as mental disorders unless they are symptoms of a "behavioral, psychological, or biological dysfunction." However, the concept of normal behavioral/psychological functioning is as hazy as that of mental disorder. Since behavioral/psychological dysfunction is often inferred from the presence of deviant behavior, it is circular to ask if deviant behavior is being caused by such a dysfunction. Thus, at the end of the definition, all that remains is the initial judgment about the presence or absence of mental disorder.

In effect, despite its long-winded approach, *DSM-III-R* ends up defining a mental disorder as that which is judged to be a mental disorder. Since the stated purpose of providing the definition is to show what "has influenced the decision to include certain conditions [in the classification] . . . and exclude others," should we conclude that the conditions judged by the compilers to be mental disorders were included and the rest excluded? If so, the statement serves its purpose, but why call it a definition?

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MAOI-Induced Hypersomnia in Patients With Bulimia

SIR: Martin H. Teicher, M.D., Ph.D., and associates (1) recently reported on eight patients receiving monoamine oxidase inhibitors (MAOIs) who experienced severe daytime somnolence as well as disturbance of nighttime sleep. I have seen similar side effects in three young women in their 20s and 30s whom I was treating for bulimia nervosa with phenelzine, 60–75 mg/day in divided doses.

As Dr. Teicher and his colleagues also described, each of my patients experienced severe daytime drowsiness to the point of interference with work. This was coupled with complaints of frequent awakening at night. Attempts to alleviate the symptoms by administering the medication either earlier or later in the day were unsuccessful. The patients were then prescribed triazolam, 0.25 mg, with the instruction to take the medication no more frequently than every other night. In each of the three cases, addition of the triazolam improved the patient's sleep at night, and the daytime drowsiness resolved.

The reason that triazolam was successful in treating this side effect in my patients but hypnotics were not successful when they were tried by Dr. Teicher and associates is not clear, but it may be related to differences in the MAOIs prescribed (most of the previously reported patients were initially taking tranylcypromine), the degree of MAO inhibition, or the diagnoses of the patients (the previously reported patients had affective disorders rather than bulimia nervosa). Nonetheless, my experience suggests that hypnotics may be useful in treating this side effect in patients taking MAOIs. Furthermore, it suggests that the daytime sedation may be a consequence of the nighttime sleep disturbance.

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GREGORY E. GRAY, M.D., PH.D.
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Sleep Disturbance in Cognitively Impaired Elderly Persons

SIR: We read with interest the article "Sleep Disorders in the Elderly" by Michael G. Moran, M.D., and colleagues (1). The sleep disorders of elderly patients who are cognitively impaired may be different from those of healthy elderly persons.

The authors described changes in sleep with aging but referred only briefly to changes seen in the cognitively impaired. They noted that the diminished proportion of REM sleep found in aging subjects tends to have a positive correlation with the level of intellectual decline or with the presence of organic mental syndrome. It was suggested that changes in neurotransmitter substances in dementing illnesses may affect patients' sleep/wake cycles.

Indeed, patients with Alzheimer's disease have shown progressive loss of phasic activity wherein the normal rhythm of sleep/wake activity is replaced by an arrhythmic and polyphasic pattern (2). Changes in sleep architecture seen in aging persons may reflect changes in neurotransmitters, since we know that neurotransmitters play a role in sleep regulation. It therefore seems likely that cognitively impaired patients may present with disorders of sleep regulation different from those found in cognitively intact elderly persons.

Dr. Moran and associates classified sleep disturbances as primary or secondary, pointing out that the causes of secondary disturbance are more common. In the cognitively impaired population, it may be difficult to obtain a reasonable history from either the patient or the caregiver. We find that the most common underlying treatable causes of sleep disturbance in this population include pain, urinary frequency, cardiac failure, delirium, and depression. An efficient assessment breaks down the sleep disturbance into five components: failure to initiate sleep, failure to maintain sleep, mixed problems, phase-shifted sleep, and sleep/wake reversal.

Sleep hygiene is an important factor in managing sleep disturbance. Many cognitively impaired individuals are institutionalized. They commonly suffer phase-advance disturbance, because they are often put to bed in the early evening hours and expected to sleep until the alloted time for their morning care. This problem can be altered by establishing routines that allow patients to sleep in a more natural cycle. It is also helpful to identify sources of disruption within the environment that may affect initiation and maintenance of sleep.

Having remedied treatable causes in the cognitively impaired patient, the clinician is left with an effective group of sedative-hypnotics to treat sleep disturbance. We concur that the goal of treatment is to improve daytime functioning. We find that the most appropriate medications are temazepam, chloral hydrate, and, interestingly, clonazepam. Low doses of trazodone may be helpful. Triazolam may be effective for problems in initiating sleep, but it is too short-acting to provide adequate sleep maintenance. We reported previously (3) that lorazepam has been associated with a high rate of falls. Flurazepam results in excessive daytime drowsiness.

Recently, the use of hypnotics in the elderly population has been criticized. However, the majority of the demented elderly are being cared for at home. Clinicians should be aware that, if indicated, the prudent use of hypnotics in this particular population may benefit both the patient and the caregiver.

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DAVID LEISHMAN, M.D.
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Dementia and Depression

SIR: Barry W. Rovner, M.D., and associates raised pertinent and provocative issues in their article on the relationship between dementia and depression (1). In explaining the much higher than normal prevalence rate of depression in dementia that they and others have found, the authors considered the possibilities 1) that there may be greater vulnerability to psychiatric illnesses including depression in patients who develop dementia and 2) that dementia may cause depression by destroying noradrenergic neurons in the locus ceruleus. There may be another explanation as well.

Depression may actually be an early and recurring noncognitive symptom of dementia, especially in depressed older patients who also show reversible cognitive impairment, the so-called depressive pseudodementia (2). Kral's finding (3) that 20 of his 22 pseudodementia patients subsequently developed permanent dementia supports this conclusion, although Post's work (4) may refute it somewhat. Indeed, Berrios (5) may have given Kral's view a historical framework by reviewing French psychiatrist Mairet's work, which challenged the nineteenth century view of a "vesanic" dementia, i.e., a dementia caused by functional psychosis.

Too persistent or vigorous a treatment of depression in such patients (with tricyclics or ECT) may well hasten the course of dementia, the very illness which we, as psychiatrists, may be seeking to deny. Also, these patients and their relatives are thus deprived of precious time and opportunity to find supportive ways of coping with the irreversible cognitive impairment when it establishes itself. One can only reaffirm Dr. Rovner and associates' exhortation to find novel ways of treating depression and dementia in the elderly.

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DILIP RAMCHANDANI, M.D.
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Psychiatric Diagnosis in China

SIR: Allow me to make a few comments on the article on mental health care in China by Lori L. Altshuler, M.D., and associates (1), which raised important psychiatric (in particular, diagnostic) issues in a cultural context—notably, a Sino-American one. The authors' observations included an impressive 89.7% agreement between American and Chinese diagnosticians. This is impressive because it is well-known that a group of well-trained psychiatrists or analysts could come up with many different diagnoses for the same patient.

Amidst the similarities were differences, however. For instance, major affective disorders (by American standards) were liable to be diagnosed by the Chinese as something other than depression, such as schizophrenia, especially if there were delusions or hallucinations; American-diagnosed depression was often diagnosed by the Chinese as anxiety disorder or neurasthenia, especially if there was a tendency toward somatization; and the Chinese noted a seemingly high rate of paranoid tendencies.

1. To begin with the last point, the finding of a high rate of paranoid states happens to agree with this writer's long-held impression of such a rate in the psychiatric patients among East Asian immigrants to America. A paranoid tendency among immigrants and minorities may be understandable and even inevitable, but this article suggested a high rate in the patients' natural habitat as did another interesting recent paper, by Fujimori et al. (2).

What may be the reasons? One cultural factor comes to mind: if a basic, conscious or unconscious, East Asian value in daily life is "social" perspective (3), a (for us) free-floating anxiety (or a free-standing depression, so to speak) can be perceived in terms of human relations. Since human relations can be considered either positive, neutral, or negative, and since future psychiatric patients are likely to have suffered from negative social experiences, especially during childhood, one of the first symptoms would be a perception of a negativity (i.e., a paranoid flavor) in human relations.

2. Neurasthenia, it has been suggested (4), is a large diagnostic basket, not only in China but elsewhere in East Asia, the contents of which are yet to be sorted out. However, fine semantic diagnostic points are not a priority issue in China at this time. Besides, given the relatively small base of modern psychiatry in China plus the fact that China's psychiatric consciousness is interspersed and irregularly layered with, to be a bit simplistic, German/Kraepelinian, Russian/Pavlovian, and, now, American/Freudian ideas, it will take time to have

a diagnostic system that is coordinated with China's tradition and appropriate to its needs.

Do the Chinese somatize more? They seem to, as their neighbors such as the Koreans do also, not because of a paucity of appropriate vocabulary and not because they are afraid to be stigmatized as "crazy" (if they are convinced that psychiatry is good for them, they will seek it out, stigmatization or not), but because the sociopsychological structure inhibits expression of anger or other disruptive feelings and thoughts in the environment, where harmony is the ideal.

3. One of the cultural values that directly impinge on psychiatric diagnostic considerations involves a generally culture-bound notion of the nature of and relation between feelings and ideas. Let me make one point about this vast and complex issue, using the term "feelings" interchangeably with "affects," "emotions," and even "intuition" and the term "ideas" with "words," "thoughts," and "intellect." I think it is reasonable to suggest that in the Confucian, Buddhist, and Hindu traditions, feelings and intuition have a higher value than words and intellect. This means that the nature of feelings and ideas and their interrelation are seen differently than they are in the West. To my knowledge, this issue has not been raised, although we all agree on the centrality of feelings and ideas as diagnostic issues.

One of the social or cultural impediments to free expression of feelings—in particular, socially disruptive ones such as anger—relates to the social ideal of harmony. Blocked in this social pathway, angry, depressive, and other related negative affects are drained off through physical channels such as somatization.

Altogether, basic psychiatric issues are importantly related to culture, and many questions are as psychological as they are philosophical. Cultural psychiatry can show us how psychiatry can be more than a follower of the culture and time.

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Psychiatric Genetics

SIR: I was delighted to read the article "Genetics and Psychiatry" (1) and to note that it had the lead position in the *Journal*'s April 1989 issue. As a researcher who has had a long-term interest in the subject, I feel that the field is finally getting the attention it deserves. I also welcome the concluding paragraph. I have been around long enough to know that, indeed, the technology available today does exceed the dreams of the early investigators.

I want to point out, however, that using their primitive research tools, the early investigators reached conclusions very similar to those offered today with regard to the role of genetic factors in the etiology and pathogenesis of schizophrenia, bipolar disorder, Alzheimer's disease, and Huntington's disease. I regret, therefore, that founders of psychiatric genetics, such as Franz J. Kallmann (my mentor), who were vilified by their colleagues in the 1940s, 1950s, and 1960s for espousing their views, were not even mentioned. Kallmann pioneered twin and family studies in the United States, and there were others here and in Europe at the time. However, the oldest reference in the article dates to 1966. Psychiatric genetics is but one illustration of the fact that major discoveries can be made with limited resources; smallpox vaccination long before the birth of modern virology is an example from another field. I believe that we can render a positive service to psychiatry by keeping new generations informed of the work that preceded theirs. Unlike Athena, knowledge does not spring forth fully formed, but builds on earlier knowledge, slowly and often painstakingly in the face of active opposition.

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The Inpatient Unit Director

SIR: I was delighted and encouraged to read the discussion by Ellen Leibenluft, M.D., and associates (1) of the plight of the inpatient unit director in the academic psychiatry department. I can only imagine a nationwide collective "amen" from those of us who have shared the experience.

My first 4 years after residency were spent in such a role. I found it an invaluable experience, and while I acknowledge some envy that others wrote this article instead of me, I think the fact that I never had the time to write it—or much else—when I was unit director only underscores the authors' points.

Inpatient unit directors have often been in the curious position of overseeing the department's most financially rewarding activities while earning little prestige in an entry-level job. At my hospital, it was necessary for the attending physician to write daily progress notes on all patients with private insurance; on a 17-bed ward, the director, therefore, spent about an hour a day charting usually redundant material previously written by the resident or medical student. Not only was this wasteful from all standpoints except the financial, but this reality also seemed to make a statement about the role of the junior faculty. Dr. Leibenluft and colleagues observed that senior faculty members tend to avoid inpatient work; somehow, the idea of a full professor writing notes in this manner seems unimaginable.

Junior faculty inpatient unit directors are often recently graduated residents. It is not uncommon for the residents they supervise to be older than they are. Most have had little training in either management or supervisory skills. Often, their professional identity is ambiguous (2), and the inpatient director's need to juggle many hats does little to resolve this. The only clear payoff for some is to concentrate on research activities; the rewards for good ward administration, teaching, or clinical skills are frequently transient and do not diminish the pressure to do quality research.

Such inpatient unit directors, even through postresidency, will benefit from formal supervision by interested, more experienced faculty members who appreciate these issues. Academic departments would be wise to incorporate this into their programs. I was fortunate enough to have had that experience, and it was extremely important and useful in identifying the innumerable developmental, administrative, clinical, political, financial, and academic issues that drive many from this critical role in academic psychiatric departments.

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RICHARD J. MOLDAWSKY, M.D.
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Dr. Omer Replies to Letters on Psychological Factors in Preterm Childbirth

SIR: Regarding the comments of Joseph A. Istvan, M.D. (1) on the article on psychological factors in preterm labor by George S. Everly, Jr., Ph.D., and myself (2), I wish to make the following points. 1) Dr. Istvan hazarded a guess that the data correlating psychopathology with preterm labor reported by Omer et al. (3) would not reach significance on a parametric test. We reanalyzed the data and found that the t values proved significant for virtually the same scales as reported originally (SCL-90 scales: depression, $t=1.70$; anxiety, $t=1.66$; paranoid ideation, $t=2.66$; psychoticism, $t=1.67$; each $p<0.05$, one-tailed). 2) Although, as Dr. Istvan suggested, people can habituate to many kinds of stress, conditions such as persistent anxiety have been consistently shown to be linked to chronic sympathetic arousal and to high muscle tension (4). 3) In order to invalidate the connection between stress/anxiety and preterm labor, it is not enough to criticize the correlational data reviewed. We have also presented data on the effectiveness of hypnotic relaxation, on laboratory activation of the uterus by frightening stimuli, and on the relationship between high muscular reactivity and pregnancy outcome.

Valerie D. Raskin, M.D. (5) posed an important question: how can our hyperreactivity model accommodate the fact that β-mimetic agents, which are often anxiety arousing, are known to be effective in preterm labor? A possible answer is that the catecholamine link between anxiety and uterine activation lies in the α receptors. Norepinephrine affects them selectively, whereas epinephrine affects both α and β receptors (with α activation growing relative to β as time goes by). Ritodrine and terbutaline, on the other hand, are selective β agonists. As for the patients who develop acute anxiety with these drugs, they may have higher chances of treatment failure, either because of concomitant uterine activation or because the drug must be stopped due to anxiety side effects.

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HAIM OMER, PH.D.
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The Modified Overt Aggression Scale

SIR: Regarding the recent critique of the Overt Aggression Scale (OAS) by Robert Scott Smith, M.D. (1), many of the criticisms leveled are valid but are rectified by setting strict limits on how the scale is to be applied and by using the Modified Overt Aggression Scale (MOAS). We are currently evaluating the validity and reliability of the modified scale and hope to report results in the near future.

Dr. Smith's major criticism was that the OAS treats its data as if they were measurable on an interval scale. He correctly pointed out that aggression does not lend itself to such measurement and that this can lead to misinterpretation. As he eloquently noted, "Does one black eye (OAS value=5) really equal three swearwords (OAS value=1) plus a mouthful of spittle (OAS value=4)?" Of course not! For this reason, the OAS should not be used to assess violence at one point in time. Used in this way, the numerical results are largely meaningless. However, the OAS and the MOAS *can* be used to assess trends in behavior over periods of time, with repeated measurements. This is similar to the use of the Glasgow Coma Scale, on which a one-time measurement of 10 is largely meaningless. For a one-time assessment, the clinician must actually know the patient's status, for instance, "Patient opens eyes to verbal commands, has fluent speech, etc." The OAS and MOAS, like the Glasgow Scale, are primarily useful for evaluating longitudinal trends.

I agree with Dr. Smith that the four behavioral subscales of the OAS and MOAS can and should be scored separately, since each subscale describes a different type of behavior. Listing scores for each subscale would allow us to make evaluations such as, "Patient X still has an overall rating of 80, but now the scores are 30-30-20-0 instead of 10-10-10-50." This is significant, since it indicates a change in pattern from physical aggression to verbal aggression.

The MOAS was developed in the course of a study to assess the effects of nadolol (a β-blocker) on aggressive behavior (paper by P. Sorgi et al. submitted for publication). During that study, the OAS was found to lack usefulness because it measures only one incident and thus needs to be filled out every time a patient displays a described behavior. On a busy psychiatric ward, where patients may be displaying the described behaviors numerous times a day, the staff simply is unable and unwilling to fill out an OAS for each incident. The MOAS is a retrospective scale, meant to cover a 1-week period of behavior. It includes the same 16 items of behavior as the OAS but does not include the section on interventions. Each of the 16 items is rated on a 5-point scale from "never" to "greater than 10 times per week." If used only to assess trends, with the knowledge that the numerical scores have specific limitations in the manner in which they can be interpreted, the MOAS will potentially fulfill the need for a scale to be, as Dr. Smith hopes, "confidently incorporated into clinical studies that test alternative interventions for aggressive behavior."

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DANIEL W. KNOEDLER, M.D.
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Dr. Smith Replies

SIR: Dr. Knoedler's forthcoming report on the MOAS should be of interest to those who intend to use the scale. His attention to OAS subscale levels permits discrimination among various patterns of aggressive behavior. His validity and reliability data should show 1) whether the milestones, which demark the levels on each of the four OAS subscales, are in fact distinct and in proper order and 2) whether different observers of the same aggressive behavior select similar subscale levels to characterize that behavior. These scaling procedures are necessary prerequisites to performing clinical studies that entail the use of ordinal statistics for comparison of OAS subscale levels.

Dr. Knoedler's retrospective reporting should be able to consider the patient who manifests a variety of aggressive behaviors over the previous week. Estimates of the frequency of each level of intensity of each type of aggression will have to be made. The merit of Dr. Knoedler's methods may then be studied by comparing the results of his retrospective reporting with those obtained from concurrent tallying of aggressive behaviors as they occur during the week.

Psychiatry will benefit from a concise, standardized scale that clinically measures aggressive behavior. Ideally, it will enhance mental status reports as well as clinical studies, analogous to the implementation of Virginia Apgar's score in pediatrics (1) and, as Dr. Knoedler points out, the Glasgow Coma Scale in neurology (2).

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ROBERT SCOTT SMITH, M.D.
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Sexual Abuse in Childhood and Freud's Seduction Theory

SIR: I have followed with great interest a series of articles that has appeared in this journal over the past 2 years concerning childhood sexual abuse of adult patients (1–3). These are part of a broader literature that includes antecedents to social deviance, chronic psychosis, and multiple personality disorder. The reports I have referenced are particularly notable for their common findings of somatoform and personality disorders in women who were sexually abused as children. In reviewing these and related articles, I was struck by the total omission of any mention of Freud's seduction theory. One would have little difficulty in classifying Freud's hysterical neurotics as somatoform and personality disorders in modern *DSM-III-R* nosology.

This omission may simply reflect an ignorance of Freud's early works. On the other hand, I am led to speculate that the reluctance to mention Freud in all of these studies may in part be due to a fear of rekindling the controversy that surrounded Jeffrey Masson in the early 1980s. Briefly, Dr. Masson held that Freud suppressed evidence in support of the seduction theory in order to improve his chances of scientific acceptance in the Victorian culture of nineteenth-century Vienna (the story of this controversy is well documented in Janet Malcolm's book [4]). The articles I have included in the references, as well as many others from this journal, have no bearing on this issue, nor do they carry with them any general implications for the etiology of neurotic complaints in adults. Rather, they simply support some of Freud's early views concerning the potential origin of symptoms in a particular population of patients (specifically, but not only, women with somatic symptoms).

As I have offered my speculations about why this omission of any reference to Freud has taken place, I would be interested to hear from the editors, authors, or readers regarding their view of this problem.

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MARK D. REGO, M.D.
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Dr. Morrison Replies

SIR: As a matter of fact, the first draft of the manuscript for my recent *Journal* article did mention the Masson controversy over Freud's repudiation of the seduction hypothesis. On the advice of reviewers, I deleted this portion of the discussion, and rightly so, I now believe; it was not particularly germane to the data. Nonetheless, the topic merits further discussion.

Individual psychiatrists may impune Masson's motivation; in reviews, some too cavalierly dismissed his book *The Assault on Truth* (1). But like him or not, we should all thank Jeffrey Masson for helping to refocus our attention on childhood molestation and its sequelae. Freud may have been half right the first time: molestation is probably associated with a variety of adult disorders, including somatization disorder, also known as hysteria. However, the relationship may not be a causal one.

I am pleased that Dr. Rego has initiated a dialogue. I hope that other discussants will support their arguments with data.

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JAMES MORRISON, M.D.
Martinez, Calif.

Depression and Negative Symptoms in Schizophrenia

SIR: The article "Postpsychotic Depression and Negative Symptoms: An Investigation of Syndromal Overlap" by Samuel G. Siris, M.D., and associates (1) addressed a very important conceptual issue in schizophrenia: the overlap of the two symptom complexes of negative symptoms and depression.

Negative symptoms have also been reported to occur frequently and with considerable severity in patients suffering from depression (2–4). In a study by our group on negative symptoms in depression and schizophrenia (4), depressed patients showed significantly higher scores than schizophrenic patients on global ratings on various subscales of the Scale for Assessment of Negative Symptoms except for alogia. However, in a comparison of the negative schizophrenia group and the depressed patients, no significant differences emerged except in anhedonia-asociality, on which the former group scored significantly higher than the latter. Interestingly, on three individual items of the Scale for Assessment of Negative Symptoms—poor eye contact, inappropriate affect, and blocking—the schizophrenic group scored significantly higher than the depressed group. All three of these symptoms are considered important symptoms of schizophrenia.

Research into whether the negative symptoms of postpsychotic depressed patients resemble more closely those of patients suffering from depression or those of patients with negative schizophrenia taken as an independent group might be helpful in solving this dilemma.

In a related field, we have done a cross-sectional study of depressive and negative symptoms in schizophrenia (5). On concurrent assessment of these two symptom complexes by independent observers, we found that a large number of patients had both negative and depressive symptoms. Of the 95 patients assessed on the Present State Examination, the Brief Psychiatric Rating Scale, and the Scale for Assessment of Negative Symptoms, only 11 had no negative symptoms and only 12 had no depressive symptoms. Although retardation, slowness, and lack of energy were more marked in the schizophrenic patients with negative symptoms, the specific symptoms of depression, such as depressed mood, hopelessness, suicidal ideation, somatic concern, and self-deprecation, had an almost equal distribution in the negative, positive, and mixed subtypes of schizophrenia. Guilt and early morning awakening were found to be uncommon. In a multiple regression analysis done to determine the strength of the relationship between negative and depressive symptoms, it was seen that except for such nonspecific depressive features as slowness, retardation, and lack of energy, other more specific symptoms of depression did not show any meaningful relation to negative symptom scores. This study showed that although negative and depressive symptoms may be similar in appearance and observable behavior, they probably originate from different underlying processes. This aspect, however, needs to be investigated further.

The improvement that Dr. Siris and his colleagues noticed in some of the patients with negative symptoms who were given imipramine is another interesting finding that needs extensive study, because until now negative symptoms have been found unresponsive to various psychopharmacological agents.

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Dr. Siris Replies

SIR: We appreciate the interest shown by Drs. Chadda and Jain in our investigation of depression and negative symptoms in schizophrenia and agree that further investigations will be required to resolve the issues that have been raised. Conceptually, much of our current difficulty stems from the facts that 1) no one can yet validate studies of schizophrenia, depression, or negative symptoms with a "tissue level" diagnosis (i.e., biopsy, autopsy, or some other truly definitive medical-diagnostic finding), and 2) many of the signs and symptoms we are assessing can represent sequelae of nonspecific dysfunction and "failure to thrive." Thus, although we find it useful heuristically to consider constructs such as depression and negative symptoms in our continuingly dysfunctional schizophrenic patients, it is also difficult for us to distinguish these states (if they are in fact as distinct as we might like to think) from such conditions as demoralization, chronic disappointment reaction, or any of the various presentations of neuroleptic-induced akinesia (1).

Nevertheless, a correct understanding of syndromes is crucial—for our understanding of pathophysiology and for appropriate treatment. Currently, we may still be somewhat confused when a construct such as negative symptoms appears to be valid yet at the same time is applicable to disparate disease states. Medicine, however, presents us with various examples of important syndromes, such as fever, that can occur across disease states but that carry their own specific pathophysiologies and their own separate implications for treatment. Some aspects of what we are currently calling "negative symptoms" may ultimately come to be understood in this context, but that is a matter which further empirical research will help us to determine.

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Prodromal Symptoms in Panic Disorder

SIR: In "Prodromal Symptoms in Panic Disorder With Agoraphobia" (1), Giovanni A. Fava, M.D., and associates reported that of 20 patients suffering from panic disorder with agoraphobia, 18 had experienced agoraphobic avoidance, generalized anxiety, and/or hypochondriacal fears and beliefs during the 6 months before the first panic attack. Normal control subjects reported significantly fewer of these phenomena in the 6 months before they had an identical interview. Dr. Fava and his colleagues concluded from these data that agoraphobic symptoms are more primary than panic attacks in panic disorder with agoraphobia—a reversal of the causal sequence assumed in *DSM-III-R*.

Imipramine's effects in agoraphobic patients originally suggested that panic attacks were the primary disturbance in most such patients and that anticipatory anxiety and agoraphobic avoidance followed as reactions to the initially unexpected anxiety episodes (2). As noted by Dr. Fava and associates, several subsequent investigations generally affirmed this phenomenological sequence.

Limiting the usefulness of the data from Dr. Fava's group are three important methodological issues. First, it is unclear whether the patients and control subjects were interviewed about prior symptoms by persons blind to diagnosis, so as to avoid investigator bias. Second, the degree of agoraphobia, generalized anxiety, or hypochondria found in the patient group before panic onset was not specified. While it appears that these levels exceeded some threshold and therefore differed from what was found in the control subjects, the investigators did not specify whether the patients suffered clinically severe agoraphobic symptoms before their panics began or whether these developed only after the onset of panic. Also, Dr. Fava and colleagues cited Weissman and Merikangas's finding (3) that a sizable percentage of agoraphobic patients in epidemiological samples did not have panic attacks, but without specifying that many of them had limited-symptom (partial panic) attacks. This does not appear to have been investigated by Dr. Fava's group.

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MICHAEL R. LIEBOWITZ, M.D.
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SIR: Dr. Fava and his colleagues reported in their article that 18 of their 20 patients suffering from panic disorder with agoraphobia experienced agoraphobic avoidance, generalized anxiety, and/or hypochondriacal fears before the first panic attack. This observation is not in accordance with the current view that the first panic attack is "a hit from the clear sky." The finding of Dr. Fava and co-workers is very important because it shows that panic disorder cannot be categorically differentiated from syndromes in which the symptoms are like those in panic disorder but the beginning is not abrupt. If this conclusion is not neglected, we have to consider anew the relationship between the symptoms and anxiety in panic disorder. Which comes first? This question was a subject of argument in the cardiologic literature on neurocirculatory asthenia (Da Costa's syndrome) from World War I to the early 1960s, and it has remained unsolved (1–4).

Neurocirculatory asthenia is a syndrome of symptoms occurring in the cardiovascular systems of patients without signs of organic disease. Anxiety and agoraphobia were also described in these patients (2), but they received less attention in cardiologic publications. The patients were divided into acute and chronic cases. The patients with the chronic form of neurocirculatory asthenia had suffered from the symptoms since childhood. The acute cases were characterized by two facts. First, the abrupt beginning of the symptoms was preceded by some kind of stressful life event, and, second, the prognosis of the acute patients was clearly better than that of the chronic patients. It has been hypothesized that the main difference between the acute and chronic patients is in their stress tolerance: for chronic neurocirculatory asthenia patients, everyday life is too stressful.

The similarity between panic disorder and the acute form of neurocirculatory asthenia is striking. If it can be shown that panic disorder patients with prodromal symptoms have a poorer prognosis than panic disorder patients without these symptoms, and if stressful life events can be found to precede the abrupt beginning of panic disorder, then one can suspect that a more or less chronic form of panic disorder can be distinguished. We think the recent observations of Dr. Fava and associates support our suspicion. If it can be accepted that panic disorder and neurocirculatory asthenia basically represent the same pathology, then the investigation of panic disorder needs reconsideration, because the psychic disorder and the effects of environmental stress need to be combined to explain the etiology of panic disorder.

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Dr. Fava and Associates Reply

SIR: Dr. Liebowitz raises some important issues about research on prodromal symptoms in panic disorder and agoraphobia. The first involves investigator bias. Obviously, in our retrospective study it was not possible for the psychologist inquiring about prodromes to be blind with respect to diagnoses. For the patients, in fact, our procedure required careful dating of the first onset of panic attacks; knowledge of the first occurrence of panic was thus a sine qua non for the investigation. As frequently observed, almost all of our patients (19 of 20) were able to recollect these attacks and state exactly when they happened. A major factor in such recollection is the "distinct quality of panic experience": as in melancholia, the quality of the panic attack is felt by the patient to be quite different from usual experiences of acute anxiety. Limited-symptom (partial) panic attacks do not share this distinct quality, and their differentiation from generalized anxiety is quite difficult.

We agree with Rosenbaum (1) that most patients with clinically significant panic attacks also suffer from limited-symptom attacks that feature only one or two physical symptoms. They may be a residual (after treatment) phenomenon (1). However, a potential etiological role of limited-symptom panic attacks in the pathogenesis of agoraphobic avoidance can hardly be claimed. Dr. Liebowitz objects that we did not include partial panic attacks in our investigation. Somatic and generalized anxiety were included, however, and are certainly preferable, as rubrics for symptoms, to the ill-defined and inferential category of limited-symptom panic attacks in *DSM-III-R*.

Finally, Dr. Liebowitz raises the issue of the clinical significance of agoraphobia, generalized anxiety, and hypochondriasis before the onset of panic attacks. Paykel's Clinical Interview for Depression (2) provides the specific intensities that were required in our study. With respect to agoraphobia, at the time of our first diagnostic assessment, most of our patients met the criteria for panic disorder with severe agoraphobic avoidance, that is, avoidance resulting in their being nearly or completely housebound or unable to leave the house unaccompanied. Before the first panic attack, agoraphobic avoidance was either mild or moderate—resulting in a constricted life style and fear of crowded places or of remaining alone at home—according to *DSM-III-R* criteria. Obviously, panic attacks worsened agoraphobic avoidance, and this was found to be true also for generalized anxiety and hypochondriasis. In this context, it is not surprising that drug treatment directed toward panic attacks may improve agoraphobic avoidance (3) or that behavioral exposure directed to agoraphobia may improve panic, hypochondriasis, and generalized anxiety (4). However, the presence of agoraphobia, hypochondriasis, and anxiety before the occurrence of panic is clear-cut if appropriate inquiries are carried out.

We find the reference of Drs. Mäntysaari and Länsimies to neurocirculatory asthenia quite appropriate. Recently, attention has been called to the presence of panic attacks in cardiology patients (5). We are currently carrying out an investigation of the psychopathology associated with neurocirculatory asthenia in patients at a university cardiology outpatient clinic. The preliminary results for 46 consecutive patients suggest that panic attacks are indeed common (5). When their presence is ascertained, Paykel's interview (2), modified for prodromal symptoms, is given. Also, when panic attacks occur in the setting of neurocirculatory asthenia, prodromal symptoms are conspicuous, lending support to our previous investigation of prodromal symptoms of panic disorder.

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ERG b-Wave Amplitude and Brain Dopaminergic Activity

SIR: Edward R. Ritvo, M.D., and associates (1) presented an intriguing study on the electroretinograms (ERGs) of 27 autistic patients and 20 healthy control subjects. The authors observed reduced b-wave amplitudes in 13 autistic subjects and a constantly low b-wave in one of these subjects during four recordings in 1 year. They drew conclusions with caution and, apart from the possible interference of technical factors that might give rise to artifacts, they hypothesized that low b-wave amplitude in autistic subjects may be associated with factors unrelated to autism, be secondary to autism, or be linked to the delays in development. They also mentioned the possible existence of retinal abnormality, which is present in strains of mutant mice showing Purkinje cell loss similar to that observed in brain samples of autistic patients at autopsy.

We would like to add that another possible explanation for such reduced ERG b-wave amplitude in autism may be related to dysfunction of the dopaminergic system. Several data suggest that ERG b-wave amplitude is a useful tool for investigating central and retinal dopaminergic activity in humans (2, 3). ERG b-wave amplitude reflects the activity of the inner nuclear layer of the retina, where dopamine is the main neurotransmitter (4). In addition, some studies (3, 5) have shown a positive relationship between ERG b-wave amplitude and the level of dopaminergic activity, which changes in response to drugs that are able to increase (bromocriptine and L-dopa) or decrease (perphenazine, haloperidol, chlorpromazine) brain dopaminergic activity. No ERG change has been observed after administration of drugs with no effect on the dopaminergic system. These data strongly indicate that dopaminergic retinal cells behave like all the other brain dopaminergic cells, and they allow us to hypothesize that ERG b-wave amplitude is a reliable instrument for investigating the dopaminergic system in vivo. It thus would be of interest to further investigate ERG b-wave and other peripheral markers of the dopaminergic system in autistic subjects.

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Drs. Yuwiler and Ritvo Reply

SIR: We appreciate the comments of Drs. Castrogiovanni and Marazziti on our study of ERG responses in autism and their suggestion that the low b-wave amplitude seen in autistic subjects may reflect dysfunction of the dopaminergic system. Their own pharmacologic studies and the literature on dopamine in amacrine and interplexiform cells (1) have led us to similar speculations.

We have more recently noted that the abnormality in b-wave amplitude in autistic subjects shows some circadian variations; it is most marked in the early morning (unpublished data). This suggests the possibility that an aberration in the melatonin-generating system may be related to the ERG abnormality. Melatonin, the major hormone of the pineal gland, undergoes a marked circadian rhythm (1) and also inhibits calcium-dependent release of dopamine in the rabbit retina (2). Melatonin production in the human adult peaks at 2:00 a.m. and is near zero during the day (3). This rhythm shows a developmental pattern that depends on maturation of noradrenergic reuptake systems (4), and in neonatal animals melatonin levels are high both day and night (5). We are currently studying the possibility that the erratic developmental course characteristic of autism is accompanied by dysregulation of pacemaker systems including the melatonin-generating system. Also, if melatonin levels are dysregulated, they could, through their effect on dopamine release, contribute to the low b-wave amplitudes we have reported in some autistic patients.

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Social Adjustment in Affective Disorders

SIR: In a recent review (1), James H. Kocsis, M.D., and Allen J. Frances, M.D., criticized the overlap between the dysthymia and the major depression symptom criteria in *DSM-III* and *DSM-III-R*, indicating that in chronic depressive patients, mild changes in only one or two symptoms could lead to a shift in diagnosis. As a result, they questioned the clinical significance of the distinction between dysthymia and double depression and raised the possibility that the high rates of double depression reported in recent studies may be an artifact of overlapping criteria. The authors' article subsequently stimulated an important discussion of the guidelines for distinguishing double depression from dysthymia (2). However, to the best of my knowledge, no data addressing the clinical significance of the distinction between dysthymia and double depression have been reported. Hence, in order to address this issue, I compared the social adjustment of patients with double depression in the dysthymic and major depressive states.

The subjects consisted of 50 consecutive outpatients meeting the *DSM-III* criteria for dysthymic disorder and a current or past major depressive episode. The sample, diagnostic procedures, and reliability of the interview data have been described previously (3). Briefly, patients received a structured diagnostic interview shortly after clinic intake. Social impairment was assessed on a 4-point global scale. Follow-up assessments, conducted 6 and 12 months later, included the Longitudinal Interval Follow-up Evaluation (4), and the Social Adjustment Scale (5). Between-subjects analyses were conducted to compare dysthymic patients who did and did not exhibit superimposed major depression both at entry into the study and at follow-up; within-subject analyses were conducted to compare patients when they were in dysthymic and in major depressive states. One-tailed independent and paired-sample t tests were used.

At entry into the study, 31 patients met the criteria for major depression. These patients exhibited significantly greater social impairment (mean±SD rating=3.19±0.87) than did the 19 subjects in a dysthymic state (2.74±0.81) ($t=1.85$, $df=48$, $p<0.05$). For the within-subject analyses, all patients who had experienced a major depressive episode during follow-up, had also met the *DSM-III* criteria for dysthymic disorder for at least 1 month, and reported being depressed most of the day more days than not but did not meet criteria for major depression, were identified (N=25). Mean global social adjustment, as assessed by the Longitudinal Interval Follow-up Evaluation, was significantly poorer during the months in which the patients experienced major depressive episodes (mean±SD score=3.87±0.62) than during the months in which they met the criteria for dysthymia (3.58±0.67) ($t=2.99$, $df=24$, $p<0.005$). Finally, the social functioning of the patients in a major depressive episode at the time of one of the follow-up assessments (N=9) was compared to that of the patients meeting the criteria for dysthymia at the time of a follow-up assessment (N=14). Patients with major depression exhibited significantly poorer global social adjustment scores on the longitudinal evaluation (mean±SD=3.89±0.69) than those in a dysthymic state (3.27±0.78) ($t=1.83$, $df=21$, $p<0.05$). Similarly, patients in a major depressive episode reported significantly greater impairment on the Social Adjustment Scale (mean±SD score=2.85±0.33) than those in a dysthymic state (2.49±0.52) ($t=1.71$, $df=21$, $p=0.05$).

These data indicate that in patients with double depression, the dysthymic and major depressive states are associated with significant differences in social adjustment. Although the distinction between dysthymia and double depression is often difficult and may, in some cases, appear arbitrary, the present findings provide support for its clinical significance.

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Dr. Kocsis Replies

SIR: Dr. Klein raises the important issue of the place of social and vocational impairment in the classification of affective disorders. The specific question addressed is the meaning of an increase in social dysfunction that is associated with an episode of major depression occurring in a patient with a history of dysthymic disorder. There are two possible interpretations of this finding. 1) Social and vocational impairment may simply be one clinical feature of dysthymic disorder. Social adjustment may fluctuate with severity of illness. Thus, a chronic dysthymia that waxes and wanes in severity might be expected to be associated with more social dysfunction during a major than during a minor phase. The major depression might merely represent a quantitative fluctuation in severity of illness and not a new and distinct diagnosis. 2) A major depression occurring in a dysthymic patient may represent a qualitatively distinct entity—a new condition superimposed on the underlying state, as implied by the term "double depression" (1). Social impairments of various types may represent symptoms specific to the major depressive disorder and separable from the symptoms of dysthymic disorder.

The data presented by Dr. Klein document an increase in global social dysfunction scores during a major depression phase, but they do not provide evidence for choosing between the two interpretations I have mentioned.

In evaluating the concept of double depression and planning the classification of mood disorders in *DSM-IV*, it would be useful to know if the more severe phases of a dysthymic disorder have distinct clinical features separable from those seen in less severe phases. It would also be useful to know whether patients with double depression differ in clinical, familial, or biological characteristics from those having chronic minor depression.

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Alprazolam Augmentation of Neuroleptics in Schizophrenia

SIR: We read with interest the recent report by Richard Douyon, M.D., and associates (1) on the beneficial effects they observed with alprazolam augmentation of neuroleptics in schizophrenic patients partially refractory to treatment. As they pointed out, there appears to be a heterogeneous response of such patients to alprazolam augmentation, with only some patients showing brisk responses. This is quite similar to data we have previously reported with alprazolam (2) and others have reported with other benzodiazepines (3). Possible sources of variance that might account for these heterogenous responses are pharmacokinetic interactions resulting in altered neuroleptic levels or differences in plasma benzodiazepine levels. Dr. Douyon and his associates found modest, nonsignificant alprazolam-associated changes in plasma neuroleptic levels, but they did find that alprazolam responders tended to have higher plasma alprazolam levels (>23 ng/ml). They raised the possibility of adjusting alprazolam doses to reach plasma levels of 60–80 ng/ml in order to maximize the likelihood of clinical response.

These authors stated that, to their knowledge, no prior studies had assessed pharmacokinetic interactions between alprazolam and neuroleptics. We would like to clarify that in our original report (2), we did examine these issues and similarly found no significant alprazolam-associated change in neuroleptic levels. Indeed, changes in plasma fluphenazine levels were not significantly correlated with changes in global psychosis ratings. We additionally reported that there was no difference in plasma alprazolam levels between responders (mean=18.32 ng/ml, range=5.3–29.3 ng/ml) and nonresponders (mean=17.26 ng/ml, range=8.5–26.0 ng/ml) and that plasma alprazolam levels were not significantly correlated with changes in psychosis or negative symptom ratings. Pertinent to this issue, Csernansky et al. (4) found an inverse correlation between plasma alprazolam levels and emotional withdrawal ratings, but that correlation was skewed by two of their 18 patients. An additional interesting point is that although Dr. Douyon and colleagues administered doses of alprazolam equivalent to those administered by us, the plasma levels we attained were substantially lower, the highest being well below the "therapeutic range" proposed by them.

These issues serve to highlight the questions that still exist regarding the possible relationship of plasma alprazolam levels to therapeutic efficacy in schizophrenia. The observation of heterogeneity of response to benzodiazepines in these patients is apparent from virtually all studies, and further research is critically needed to determine which otherwise treatment-resistant patients might respond to these interventions.

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Dr. Douyon and Associates Reply

SIR: Our manuscript was submitted for publication in March 1988, and the article by Dr. Wolkowitz and his colleagues was published in July 1988. Our final submission was at the end of July 1988, and at that time we revised our paper to include references to the recent publication by Dr. Wolkowitz and colleagues. However, apparently, we did not read the article closely enough. These investigators are indeed correct in saying that in their article they reported that 1) alprazolam did not increase plasma fluphenazine levels, 2) changes in plasma fluphenazine levels did not correlate with changes in psychosis, and 3) the plasma alprazolam levels did not correlate with changes in psychopathology. The point that alprazolam responders and nonresponders did not differ in their plasma alprazolam levels was not made explicitly but could (and should) have been calculated from their table. We apologize for the oversight in neglecting to cite these pharmacokinetic data.

We agree that our alprazolam plasma levels tended to be higher despite roughly similar doses. The cause for this is not clear at this time; patient differences or laboratory differences will need further evaluation.

We also agree with Dr. Wolkowitz and associates that the heterogeneity of response to the benzodiazepines in schizophrenia and the possible relationship of alprazolam plasma levels to therapeutic efficacy are "questions that still exist." Our sample of nine patients is certainly not a database that can resolve these issues.

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Religiousness and Psychiatric Disorders

SIR: In their article "Religious Beliefs and Practices Among 52 Psychiatric Inpatients in Minnesota" (1), Jerome Kroll, M.D., and William Sheehan, M.D., described as "somewhat surprising" their finding that "the patients with major depression and anxiety disorders contained the lowest percentage of believers in God." Although the socioeconomic status of the participants in the study was not correlated with their illness or religious beliefs, the result the authors noted appears in all respects consistent with previous sociological and epidemiological research relating socioeconomic status to mental illness and religiousness.

Specifically, epidemiological research clearly reveals that affective and anxiety disorders are more common in the upper and middle classes (2). Hollingshead and Redlich (3) found that the prevalence of anxiety disorders increased with social class, with the highest proportion in the upper-middle class. Meanwhile, Wimberley (4), in a study of religiousness and occupational prestige and income, found an expected negative correlation. Hybridizing both findings, one would not be surprised to find less religiousness among patients suffering from anxiety or affective disorders than among those who have other psychiatric illnesses.

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Drs. Kroll and Sheehan Reply

SIR: The data Dr. Tobak cites may be suggestive of the conclusions he draws from them. To address the issue properly, however, would require a multivariate analysis of the data, rather than the kind of logic that combines 1) the statement that depressive disorders are more common in upper and middle classes with 2) the statement that religiousness is more common in lower and lower-middle classes to conclude 3) that depressed people are less religious.

Dr. Tobak should not wonder at our surprise that "the patients with major depression and anxiety disorders contained the lowest percentage of believers in God" or were the least preoccupied with guilt. The relationship of guilt to "neurotic suffering" has long been a cornerstone of psychoanalytic theory (1). The view is no doubt widespread—perhaps especially among health professionals—that religiousness is associated with (if not, indeed, a symptom of) psychopathology, yet we found evidence for neither. We hope that our article suggests that the religious attitudes of patients are open to, and merit, scientific investigation. Such investigation should replace adherence to prejudicial and pejorative notions about an area that is obviously of active interest to the majority of our patients.

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Chocolate: Pleasure or Pain?

SIR: The uses and misuses of mood- or behavior-altering drugs are major issues in contemporary society. A recent report (1) described a new and potentially dangerous drug effect: two patients were cured of their craving for chocolate! There are grave implications for society.

Consider the enormous industry supported by those for whom the daily consumption of chocolate is, if not an obsession, at least a habit. A certain city in Pennsylvania might suffer economic collapse if this drug were to exert its effect widely. Imagine the possible conspiracy between the manufacturers of other sweets (e.g., orange slices and mints)! This drug might be promoted quietly for other purposes. Would there be a public outcry as people realized that they no longer derived pleasure from chocolate? Might the effect be so subtle that it would be noticed only by Wall Street, mystified by the precipitous decline in "chocolate stocks"?

What would those of us who derive a significant proportion of our daily pleasure from chocolate do with our unsatisfied hedonistic impulses? Some might go into deep depression. Others might abandon their pleasure-seeking, carefree lifestyles and undertake new and potentially dangerous behaviors such as hard work. I do not know how many people choose chocolate in preference to sex. Imagine, however, the possible "baby boom" of unknown magnitude and economic consequence if these people were deprived of their craving for chocolate. Another group of "chocoholics" might turn to healthy activities such as exercise! The unexpected shock of such activities might prove detrimental either physically or emotionally in this subset of people who characteristically have sought to satisfy the pleasure principle in a single-minded and monolithic fashion. An indeterminate percentage might even seize the opportunity to try to achieve some insight into their feelings.

These approaches to compensation for chocolate loss might be healthy and productive in the long run but probably would require early and intensive psychiatric care. Given the magnitude of chocolate craving in our society, I am not sure that adequate numbers of qualified psychiatrists are available to meet the demand.

The total cost of appropriate medical care could well exceed the cost of the original chocolate!

A larger issue concerns other drugs that could alter our daily quest for happiness. Creative pharmacology knows no bounds. What is next on the list? Orange juice? Ice cream? Might we soon see a drug that cures people of pleasure from high-cholesterol foods such as red meat and cheese? Is the state of our health and the quality of our life up to us? Or are we to be manipulated pharmacologically by unknown masters deciding what balance of health and pleasure is good for us? This Orwellian domination is dangerous to our concept of individual responsibility and freedom of choice.

Admitting a personal bias, I respectfully suggest that this new antichocolate drug is dangerous to our health and likely to increase the cost of medical care. Therefore I recommend that the Food and Drug Administration ban this medication or, at the very least, make it a class II prescription drug.

REFERENCE

1. Michell GF, Mebane AH, Billings CK: Effect of bupropion on chocolate craving (letter). Am J Psychiatry 1989; 146:119–120

HERBERT RAKATANSKY, M.D.
Providence, R.I.

Dr. Michell and Associates Reply

SIR: We thank Dr. Rakatansky for his comments on our report on the antichocolate effect of bupropion. We were aware that our observation might have serious implications for "a certain city in Pennsylvania," but we may have underestimated the potential for the unleashing of unsatisfied hedonistic impulses in deprived chocoholics! However, let's not forget those countless obese individuals who, in the grip of an unrelenting chocolate addiction, may at long last regain control of their lives. As Dr. Rakatansky suggests, these are the people who might turn to healthy activities such as exercise!

Dr. Rakatansky's concern about Orwellian domination is perhaps an exaggeration, but we will concede that the Food and Drug Administration should set a precedent here. We propose that pharmacists be required to clearly label all filled bupropion prescriptions as follows: "Use of this drug may seriously alter your freedom to derive pleasure from eating chocolate products, which could lead to a drastic change in lifestyle." We hope that such a warning will allay anticipatory anxiety concerning this dangerous drug effect and will lead to informed consent by potential victims of this effect.

GARY F. MICHELL, M.S.
ANDREW H. MEBANE, M.D.
CHARLES K. BILLINGS, M.D.
New Orleans, La.

Correction

In the article "A Comparison of Three Measures for the Diagnosis of Borderline Personality Disorder" (November 1988 issue, pp. 1453–1454) by Lynne E. Angus, Ph.D., and Elsa Marziali, Ph.D., the percent for Diagnostic Interview for Borderline Patients, near the end of the first paragraph on p. 1454, should be 70%.

Reprints of letters to the Editor are not available.

1988–1989 Annual Report of the American Board of Psychiatry and Neurology, Inc.

Composition of the Board

At its business meeting on Oct. 15, 1988, the American Board of Psychiatry and Neurology (ABPN) elected the following officers, who began their terms on Jan. 1, 1989: Dr. Jack Whisnant, President; Dr. Layton McCurdy, Vice-President; Dr. Elliott L. Mancall, Secretary; Dr. Maurice J. Martin, Treasurer; and Dr. William E. Bell, Executive Committee Member-at-Large.

Dr. Mark L. Dyken, Jr. (Indianapolis), nominated by the American Academy of Neurology, was elected to a 4-year term on the Board to succeed Dr. Robert Fishman, who completed his second 4-year term on the Board on Dec. 31, 1988. Dr. Gary Tucker (psychiatrist), nominated by the American Psychiatric Association, and Dr. J. Donald Easton (neurologist), nominated by the American Neurological Association, were renominated and reelected to serve second 4-year terms as Directors. The names of the 1989 ABPN Directors follow; those serving second 4-year terms are not eligible for reelection.

Nominated by the American Medical Association (psychiatry Directors): Dr. Maurice J. Martin (second term expires Dec. 31, 1991), Dr. John F. McDermott, Jr. (second term expires Dec. 31, 1990), and Dr. William L. Webb, Jr. (second term expires Dec. 31, 1989).

Nominated by the American Psychiatric Association (psychiatry Directors): Dr. Layton McCurdy (second term expires Dec. 31, 1990), Dr. Robert Michels (second term expires Dec. 31, 1989), Dr. James H. Shore, M.D. (first term expires Dec. 31, 1990), Dr. Lenore C. Terr (first term expires Dec. 31, 1991), and Dr. Gary J. Tucker (second term expires Dec. 31, 1992).

Nominated by the American Neurological Association (neurology Directors): Dr. William E. Bell (second term expires Dec. 31, 1991), Dr. J. Donald Easton (second term expires Dec. 31, 1992), Dr. Ludwig Gutmann (first term expires Dec. 31, 1990), and Dr. Stuart A. Schneck (first term expires Dec. 31, 1989).

Nominated by the American Academy of Neurology (neurology Directors): Dr. Mark L. Dyken, Jr. (first term expires Dec. 31, 1992), Dr. Elliott L. Mancall (second term expires Dec. 31, 1990), Dr. N. Paul Rosman (second term expires Dec. 31, 1990), and Dr. Jack P. Whisnant (second term expires Dec. 31, 1990).

Dr. Stephen C. Scheiber is the Executive Secretary of the ABPN.

Examinations

Part I. At the part I (written) examination on April 4, 1989, 1,946 psychiatrists were examined; 1,203 (61.8%) passed and 743 (38.2%) failed. A total of 779 neurologists (including child neurologists) were examined; 460 (59.1%) passed and 319 (40.9%) failed. Table 1 contains the numbers of candidates in each year from 1984 to 1989. The next part I examination will be held on April 3, 1990. Applications for that examination are due no later than Sept. 1, 1989, and are available from the American Board of Psychiatry and Neurology, Inc., 500 Lake Cook Rd., Suite 335, Deerfield, IL 60015.

Part II. At the 1988 part II (oral) examinations held in San Francisco (March 6–8), Kansas City (June 12–14), and Chicago (Oct. 16–18), 1,434 psychiatrists, 419 neurologists, and 56 child neurologists were examined. For statistics on these examinations, refer to table 2. The examination sites for 1989 are Baltimore (April 9–11), Denver (weekend exam, June 9–11), and Boston (Nov. 12–14).

TABLE 1. Candidates for ABPN Part I (Written) Examination, 1984–1989

	Number of Candidates					
Physician Status	1984	1985	1986	1987	1988	1989
Met requirements	2,029	2,506	2,703	2,649	2,861	3,134
Accepted examination	1,929	2,409	2,574	2,477	2,782	3,092
Appeared for examination	1,738	2,167	2,301	2,255	2,471	2,725

The current fees for examination are as follows: part I examination fee=$550, part I reexamination fee=$300, part II examination fee=$400, part II reexamination fee (failure of major or major and minor)=$400, part II reexamination fee (failure of minor)=$300.

Board Decisions and Items of Interest

1. Effective Nov. 11, 1989, the ABPN's telephone area code will change from 312 to 708. The new telephone number will be (708) 945-7900. As of that date, the area code for suburban cities which currently have the 312 area code will change and Chicago will be the only city retaining the 312 area code.

2. The ABPN reaffirmed its policy whereby all licensing and training requirements must be met before application for examination. The only exception is for residents who complete training after Sept. 1 but before Oct. 1. Such applicants may submit an application by the Sept. 1 deadline only if they contact the Board office in writing before July 1 to obtain information regarding special application procedures.

3. The ABPN reaffirmed its policy whereby every applicant must have an *unlimited* license to practice medicine in a state, commonwealth, or territory of the United States or a province of Canada. Every applicant is required to submit copies of current license registrations and expiration dates with the application, in addition to documentation of all training.

4. The ABPN reaffirmed that it does not dictate a parental leave policy but leaves it to the discretion of the individual program.

5. The ABPN reaffirmed its policy that beginning July 1, 1988, all osteopathic physicians entering a postgraduate year 2 program in psychiatry or neurology must have successfully completed postgraduate year 1 in a program approved by the Accreditation Council for Graduate Medical Education, as described in the ABPN "Information for Applicants" pamphlet, which is available from the Board office.

6. The ABPN made the following changes in the neurology training requirements. a) Physicians may enter neurology residency (postgraduate year 2) training as of July 1, 1987, and before July 1, 1991,

TABLE 2. Performance of Physicians Who Took ABPN Part II (Oral) Examinations in 1988

	Total					Graduates of Schools in U.S. or Canada					Graduates of Foreign Medical Schools				
		Passed and Were Certified		Failed			Passed and Were Certified		Failed			Passed and Were Certified		Failed	
Candidate Group	N	N	%	N	%	N	N	%	N	%	N	N	%	N	%
All specialties	1,909	1,190	62	719	38	1,446	999	69	447	31	463	191	41	272	59
New	1,265	875	69	390	31	1,046	751	72	295	28	219	124	57	95	43
Reexamined	644	315	49	329	51	400	248	62	152	38	244	67	27	177	73
Psychiatry	1,434	881	61	553	39	1,077	745	69	332	31	357	136	38	221	62
New	928	645	70	283	30	776	564	73	212	27	152	81	53	71	47
Reexamined	506	236	47	270	53	301	181	60	120	40	205	55	27	150	73
Neurology	419	269	64	150	36	330	226	68	104	32	89	43	48	46	52
New	301	207	69	94	31	246	172	70	74	30	55	35	64	20	36
Reexamined	118	62	53	56	47	84	54	64	30	36	34	8	24	26	76
Child neurology	56	40	71	16	29	39	28	72	11	28	17	12	71	5	29
New	36	23	64	13	36	24	15	63	9	38	12	8	67	4	33
Reexamined	20	17	85	3	15	15	13	87	2	13	5	4	80	1	20

only after an initial first year of graduate training in the United States or Canada in accredited programs in internal medicine or in transitional programs that are approved by the Accreditation Council for Graduate Medical Education and include at least 6 months of experience in internal medicine. In lieu of such training during postgraduate year 1, the certifications specified in b) and c) will be accepted. b) Physicians may enter neurology residency training as of July 1, 1991, only after an initial first year of graduate training in accredited programs in the United States or Canada. It is strongly suggested that this full year consist of training in internal medicine. An acceptable but less desirable alternative is a full year in which a minimum of 8 months of training is in internal medicine, the details of which must be documented by the internal medicine training director. The composition of these 8 months cannot include rotations in neurology or emergency medicine. To ensure that these 8 months constitute a high-quality experience, emphasis should be placed on progressive responsibility for the resident. In lieu of such training in the first postgraduate year, the certifications listed in c) would be accepted. c) The certifications mentioned in a) and b) are M.R.C.P.(U.K.)—United Kingdom's Member of the Royal College of Physicians; F.R.A.A.C.P.—Australia and New Zealand's Fellow of the Royal Australasian College of Physicians; M.R.C.P.(S.A.)—South Africa's Member of the Royal College of Physicians; M.R.C.P.(I)—Ireland's Member of the Royal College of Physicians. This does not represent a total description of neurology training requirements, only those which changed.

7. The ABPN passed a motion that applicants for certification in neurology with special qualification in child neurology who begin residency training at the second postgraduate year level as of July 1, 1991, must complete their child neurology training in child neurology programs approved by the Accreditation Council for Graduate Medical Education.

8. The ABPN is proceeding with plans to offer examination for certification in psychiatry with added qualification in geriatric psychiatry. The American Board of Medical Specialties will be voting on the request at the annual meeting in September 1989.

9. The Board is holding a national conference July 22–23, 1989, to focus on certification and recertification with an emphasis on lifetime learning and the educational process. Several organizations have been invited to send representatives to participate in the conference.

10. At the 1988 APA annual meeting, the ABPN again offered a workshop titled "ABPN and RRC Update." Members of the Residency Review Committee joined the ABPN psychiatry Directors to present information about both bodies and to respond to questions. In addition, the Executive Secretary and psychiatry Directors have participated in plenary sessions and other workshops of APA and the American Association of Directors of Psychiatric Residency Training in an attempt to clarify information and to publicize current issues of interest. A workshop will also be held at the 1989 APA annual meeting that will focus on recertification.

TABLE 3. Performance of Physicians Who Took Oral Examinations in Child and Adolescent Psychiatry in 1988

	Total		Graduates of Schools in U.S. or Canada		Graduates of Foreign Medical Schools	
Candidate Group and Performance	N	%	N	%	N	%
Total	179	100	138	77	41	23
Pass	94	53	82	59	12	29
Condition	32	18	25	18	7	17
Fail	35	20	20	14	15	37
Fail, must reapply	18	10	11	8	7	17
New candidates	144	80	114	79	30	21
Pass	77	53	69	61	8	27
Condition	32	22	25	22	7	23
Fail	35	24	20	18	15	50
Reexamined candidates	35	20	24	69	11	31
Pass	17	49	13	54	4	36
Fail, must reapply	18	51	11	46	7	64

11. At the fall 1988 meeting of the American Neurological Association and the spring 1989 meeting of the American Academy of Neurology, ABPN neurology Directors and the Executive Secretary met with the Association of University Professors of Neurology to discuss current issues of the Board and to respond to questions. This meeting proved valuable in outlining the Board's current policies and training requirements. The issue of recertification was a key point of discussion, as was advising the Association of University Professors of Neurology of deliberations regarding possible Board designation of neurophysiology as a subspecialty.

12. The Board is participating in the American Board of Medical Specialties' review of previous part I written examinations to identify questions for which incorrect answers would be considered dangerous in clinical practice.

13. The Board history continues to be updated by Dr. Marc Hollender, who is being assisted by Drs. S. Mouchly Small, William Bell, William Webb, Dewey Ziegler, James Sussex, Helen Beiser, and John Kurtzke.

Committee on Certification in Child and Adolescent Psychiatry

Members of the Committee on Certification in Child and Adolescent Psychiatry are elected to serve one 6-year term and are not eligible for reelection. The members of the 1989 Committee on Certification in Child and Adolescent Psychiatry are Dr. Joseph Fischhoff, Chair (term expires Dec. 31, 1989); Dr. Joel P. Zrull, Vice-Chair (term expires Dec. 31, 1991); Dr. Lois T. Flaherty, Secretary-Treasurer (term expires Dec. 31, 1993); Dr. Catherine DeAngelis (representative from the American Board of Pediatrics) (term expires Dec. 31, 1994); Dr. Kenneth Robson (term expires Dec. 31, 1994); Dr. William H. Sack (term expires Dec. 31, 1992); and Dr. Theodore Shapiro (term expires Dec. 31, 1993).

At its Sept. 23–25, 1988, examination in Washington, D.C., the Committee on Certification in Child and Adolescent Psychiatry examined 179 candidates; 94 (53%) passed, 32 (18%) conditioned the examination, and 53 (30%) failed. For additional statistics refer to table 3. The 1989 examination will be held Sept. 15–17, 1989, in Atlanta. The 1990 examination will be held Sept. 6–9, 1990, in Denver. Applications are due the May 1 preceding the examination and are available from the Board office.

The current fees for examination are as follows: application fee=$225, oral examination fee=$450, oral reexamination fee (condition)=$350, oral reexamination fee (failure)=$450, written examination or reexamination=$275.

Applicants are required to submit copies of current license registrations and expiration dates with their applications, in addition to documentation of all training. All licensing and training requirements must be met before application for examination.

Other items of interest and decisions made by the Committee on Certification in Child and Adolescent Psychiatry are as follows:

1. The committee nominated Dr. Catherine DeAngelis (Baltimore) to succeed Dr. Iris Litt as the representative from the American Board of Pediatrics to the committee, effective Jan. 1, 1989, and Dr. Thomas Haizlip (Chapel Hill, N.C.) to succeed Dr. Donald S. Gair as a member of the committee, effective Jan. 1, 1990. The ABPN has approved both nominations.
2. The committee continues to arrange examinations in a weekend format. This format has been received positively by an overwhelming majority of candidates, examiners, and host facilities.
3. The committee noted difficulties with certificates issued to residents. If child psychiatry training is done during general residency it must be designated as such.
4. The committee hopes to hold an open question and answer session with training directors at the Academy of Child and Adolescent Psychiatry meeting.

STEPHEN C. SCHEIBER, M.D.
Executive Secretary

Director of Adult Mental Health Services

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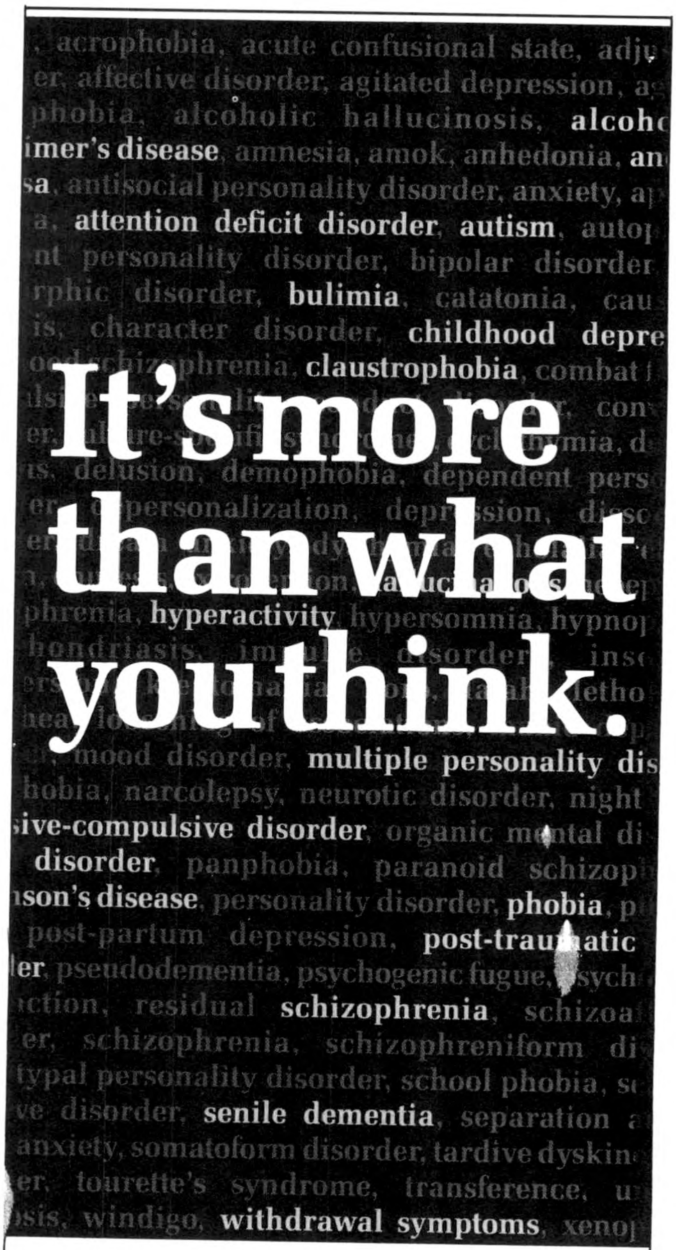
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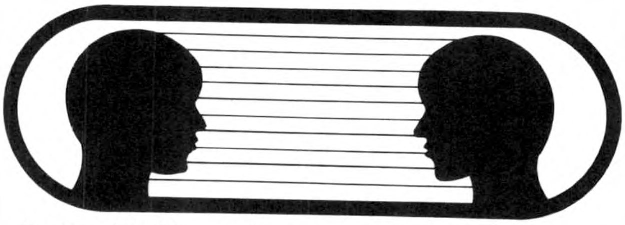

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Mr. Ron Clark
Director of Human Resources
Yarmouth Regional Hospital
60 Vancouver Street
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THE BRITISH JOURNAL OF PSYCHIATRY

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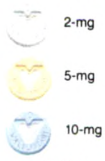

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INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

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Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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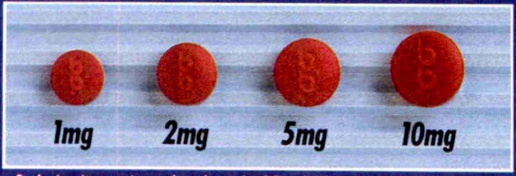

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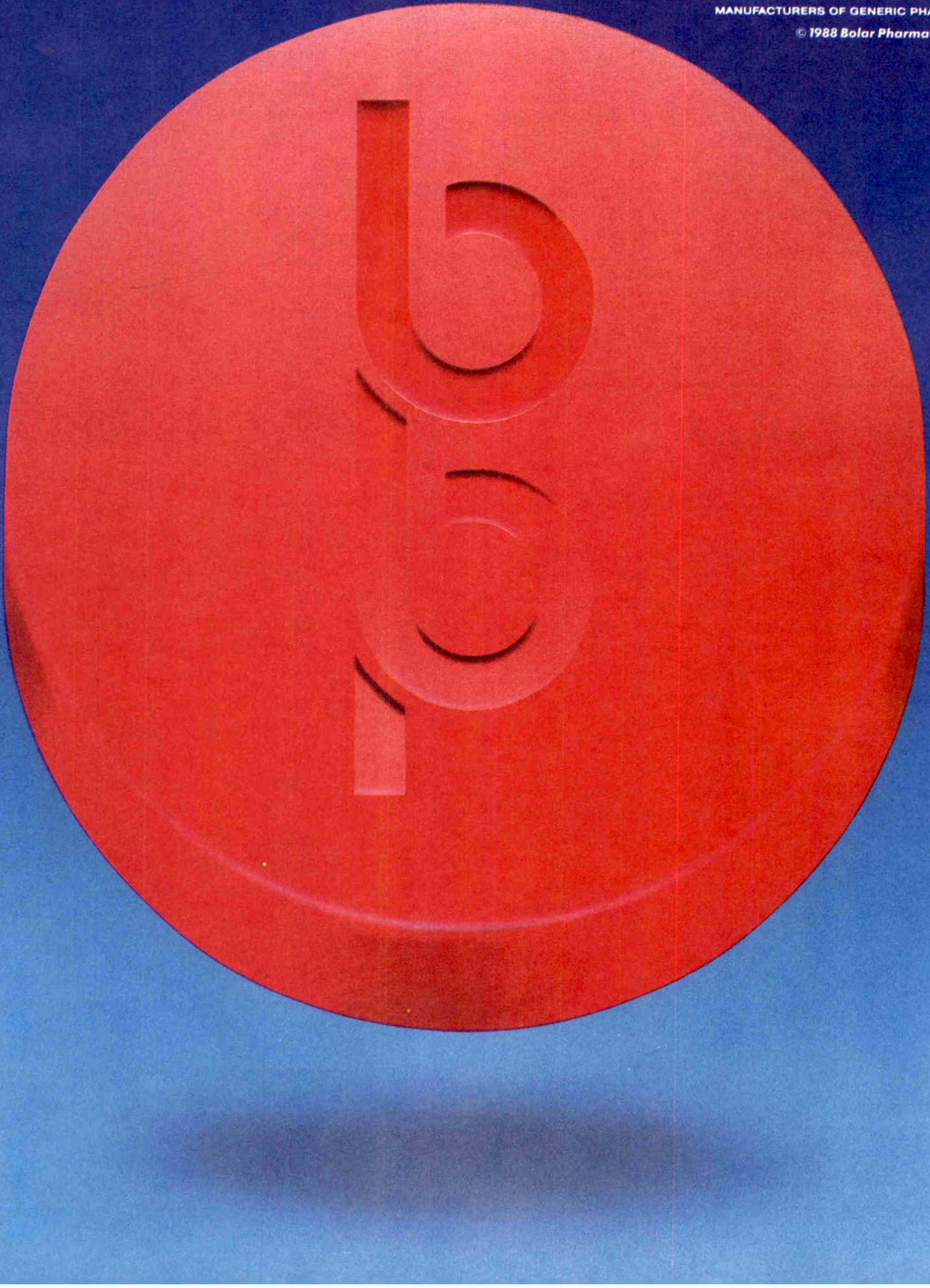

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2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

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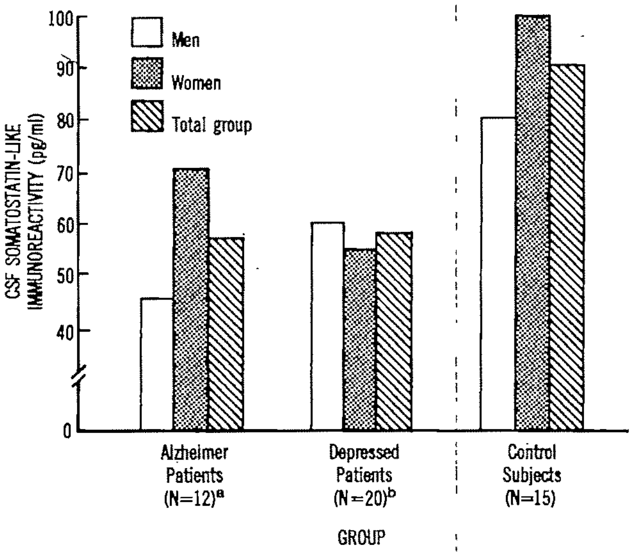
FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



[a] Significant difference between men and women ($t=1.81$, $df=10$, $p<0.05$) and between the total Alzheimer's disease group and the total control group ($t=2.49$, $df=25$, $p<0.01$).

[b] Significant difference between the total depressed group and the total control group ($t=2.75$, $df=33$, $p<0.005$).

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When Psychotic Features Complicate Depression

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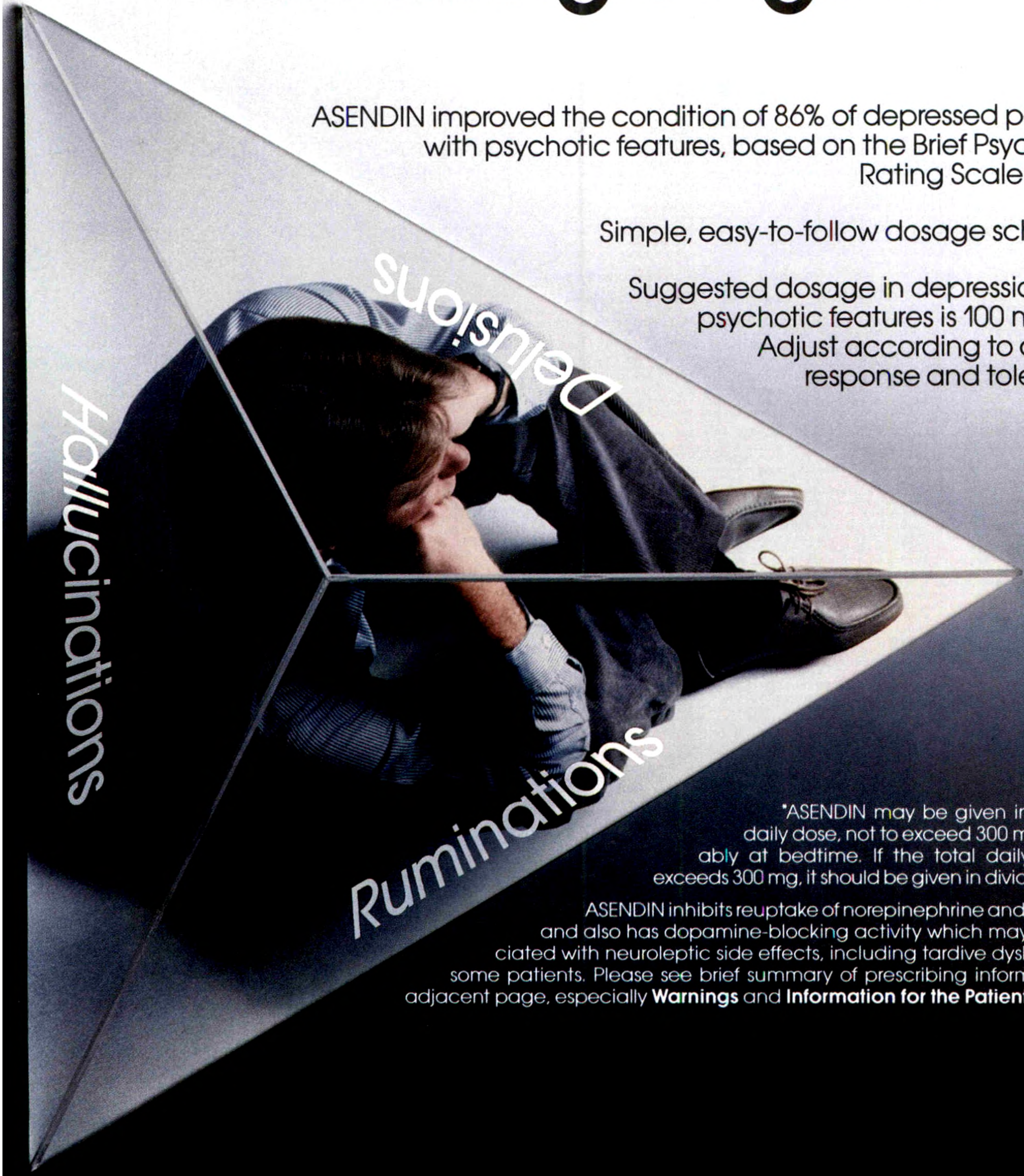

ASENDIN improved the condition of 86% of depressed patients with psychotic features, based on the Brief Psychiatric Rating Scale (BPRS)[1]

Simple, easy-to-follow dosage schedule

Suggested dosage in depression with psychotic features is 100 mg bid. Adjust according to clinical response and tolerance*

*ASENDIN may be given in a single daily dose, not to exceed 300 mg, preferably at bedtime. If the total daily dosage exceeds 300 mg, it should be given in divided doses.

ASENDIN inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects, including tardive dyskinesia, in some patients. Please see brief summary of prescribing information on adjacent page, especially **Warnings** and **Information for the Patient** sections.

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LINICAL PHARMACOLOGY

ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not ell understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of opamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost cometely metabolized. The main route of excretion is the kidney. *In vitro* tests show that amoxapine binding to human serum is pproximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major etabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. e initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

DICATIONS

ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as ndogenous and psychotic depressions and depression accompanied by anxiety or agitation.

ONTRAINDICATIONS

Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do ot give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monomine oxidase inhibitor with ASENDIN allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in osage until optimum response is achieved.

ARNINGS

ardive Dyskinesia: Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, ay develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has subantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially derly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which atients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the uration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the ndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or comletely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the gns and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomtic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of rdive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness at (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful eatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest uration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should e reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. owever, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on **formation for the Patient** and **ADVERSE REACTIONS.**)

eptic Malignant Syndrome (NMS): A potentially fatal symptom complex, NMS has been reported in association with ntipsychotic drugs. Clinical manifestations are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autoomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Diagnosis is complicated. Rule out serious medical illness (eg, pneumonia, systemic infection) and inadequately treated extrapyramidal ymptoms (EPS). Other considerations in differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, nd primary central nervous system (CNS) pathology. Management of NMS includes immediate discontinuation of antipsyhotic and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and eatment of concomitant serious medical problems for which specific treatments are available. Reintroduction of antipsyhotic drug treatment after recovery from NMS should be carefully considered and closely monitored since recurrences of MS have been reported.

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. atch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus chycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs f this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

ECAUTIONS

eneral: Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the rug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased ymptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of osage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur durg the first few days of treatment, but may also occur later. ASENDIN amoxapine should be discontinued if rash and/or fever evelop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in <1% f patients. Rarely, symptoms indicative of tardive dyskinesia have been reported. **Information for the Patient:** It is advised at all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive yskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile r operating machinery may be impaired. **Drug Interactions:** See **CONTRAINDICATIONS** regarding concurrent usage of triyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in ombination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other NS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when imetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific teraction studies have not been done, and the possibility should be considered. **Therapeutic Interactions:** Concurrent dministration with electroshock may increase hazards associated with such therapy. **Carcinogenesis, Impairment of Fertility:** In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased ncidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose roup only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings o man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of ferle matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle ength. **Pregnancy:** *Pregnancy Category C:* Studies performed in mice, rats, and rabbits have demonstrated no evidence of eratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human ose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 imes the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 imes the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used durg pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** ASENDIN, like many other sysemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when SENDIN is administered to nursing women. **Pediatric Use:** Safety and effectiveness in children below the age of 16 have not een established.

DVERSE REACTIONS

Reported in Controlled Studies: **Incidence Greater than 1%:** Most frequent were sedative and anticholinergic: drowsiness 14%), dry mouth (14%), constipation (12%), and blurred vision (7%).

Less frequently reported reactions were: *CNS and Neuromuscular:* anxiety, insomnia, restlessness, nervousness, palpitations, remors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns. *Allergic:* edema, skin rash. *Endocrine:* elevation f prolactin levels. *Gastrointestinal:* nausea. *Other:* dizziness, headache, fatigue, weakness, excessive appetite, increased perpiration. **Incidence Less than 1%:** *Anticholinergic:* disturbances of accommodation, mydriasis, delayed micturition, urinary etention, nasal stuffiness. *Cardiovascular:* hypotension, hypertension, syncope, tachycardia. *Allergic:* drug fever, urticaria, hotosensitization, pruritus, rarely, vasculitis, hepatitis. *CNS and Neuromuscular:* tingling, paresthesias of the extremities, tinnius, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal ymptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported. (See **WARNINGS.**) *Hemaologic:* leukopenia, agranulocytosis. *Gastrointestinal:* epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, iarrhea. *Endocrine:* increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea n the female, syndrome of inappropriate antidiuretic hormone secretion. *Other:* lacrimation, weight gain or loss, altered liver unction, painful ejaculation. **Drug Relationship Unknown:** Reported rarely, but under circumstances where drug relationship as unknown: *Anticholinergic:* paralytic ileus. *Cardiovascular:* atrial arrhythmias (including atrial fibrillation), myocardial infarcion, stroke, heart block. *CNS and Neuromuscular:* hallucinations. *Hematologic:* thrombocytopenia, eosinophilia, purpura, etechiae. *Gastrointestinal:* parotid swelling. *Endocrine:* change in blood glucose levels. *Other:* pancreatitis, hepatitis, aundice, urinary frequency, testicular swelling, anorexia, alopecia. **Additional Adverse Reactions:** Reported with other ntidepressant drugs, but not with ASENDIN. *Anticholinergic:* sublingual adenitis, dilation of the urinary tract. *CNS and euromuscular:* delusions. *Gastrointestinal:* stomatitis, black tongue. *Endocrine:* gynecomastia.

VERDOSAGE

igns and Symptoms: Toxic manifestations of ASENDIN overdosage differ significantly from those of other tricyclic antidepresants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—ccur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may evelop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN verdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have expernced multiple seizures. **Treatment:** Treatment of ASENDIN overdosage should be symptomatic and supportive, but with speial attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as ntravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, equires vigorous treatment such as that described by Delgado-Escueta, et al (*N Engl J Med* 1982; 306:1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant nedication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for nondrugnduced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG ypically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is *not* a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neuroogic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 11/87

1. Anton RE Hitri A, Diamond BL, et al: Amoxapine treatment of psychotic depression: Dose effect and dopamine blockade. J Clin *Psychiatry Monograph* 1986;4:32-36.

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AUGUST 1989

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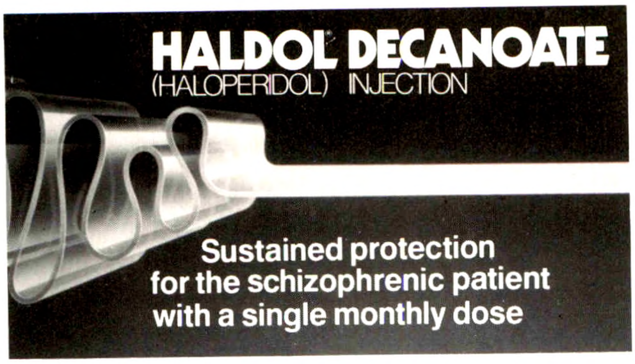
HALDOL DECANOATE

(HALOPERIDOL) INJECTION



The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5, 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear. As with other antipsychotic agents, it should be noted that HALDOL may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Tardive Dystonia*—Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL. (See WARNINGS for further information concerning NMS.) *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

7/20/88

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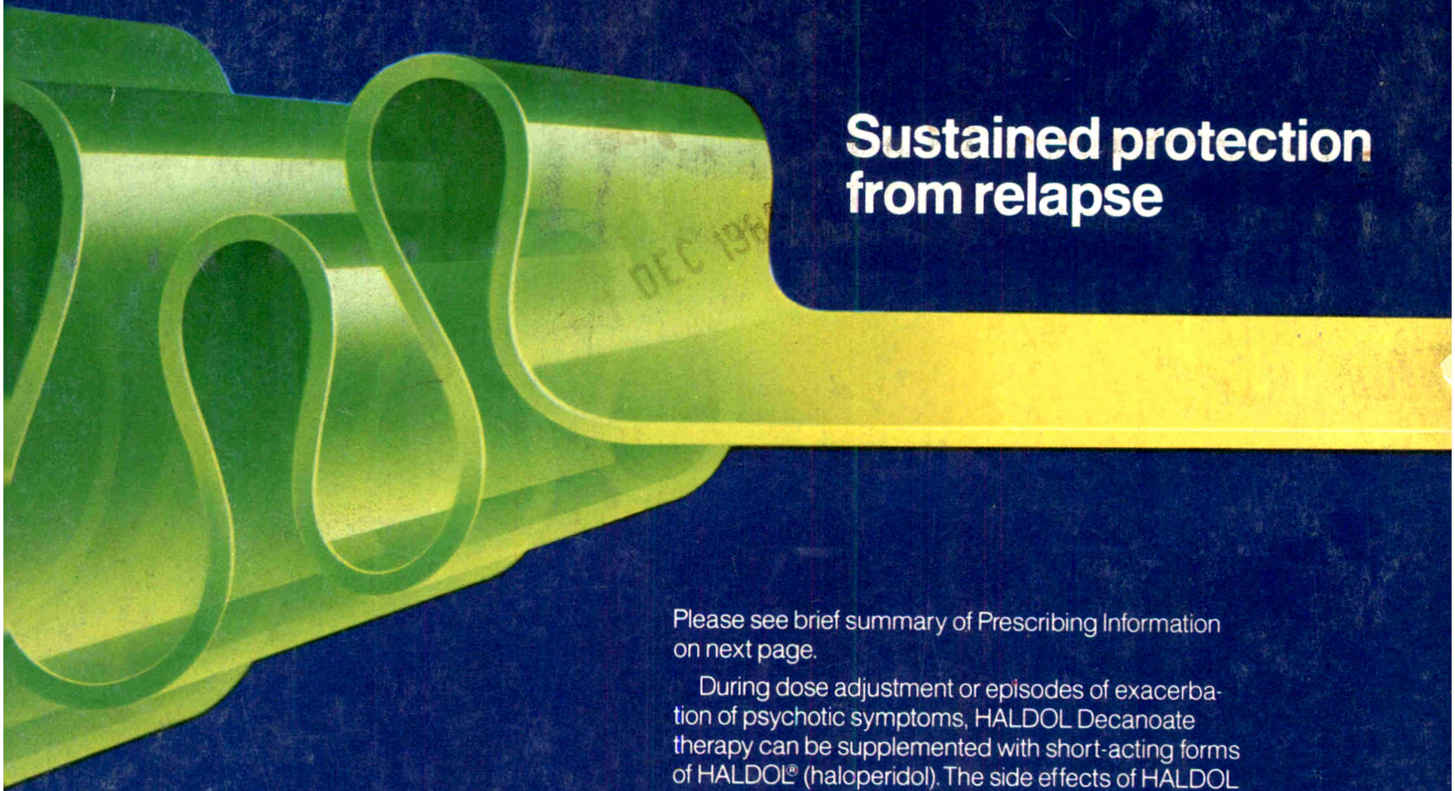

DEC 198

Sustained protection from relapse

Please see brief summary of Prescribing Information on next page.

During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL® (haloperidol). The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects.

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- ■ Medically necessary
- ■ Brand necessary
- ■ May not substitute
- ■ No substitution
- ■ NDPS (no drug product selection)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

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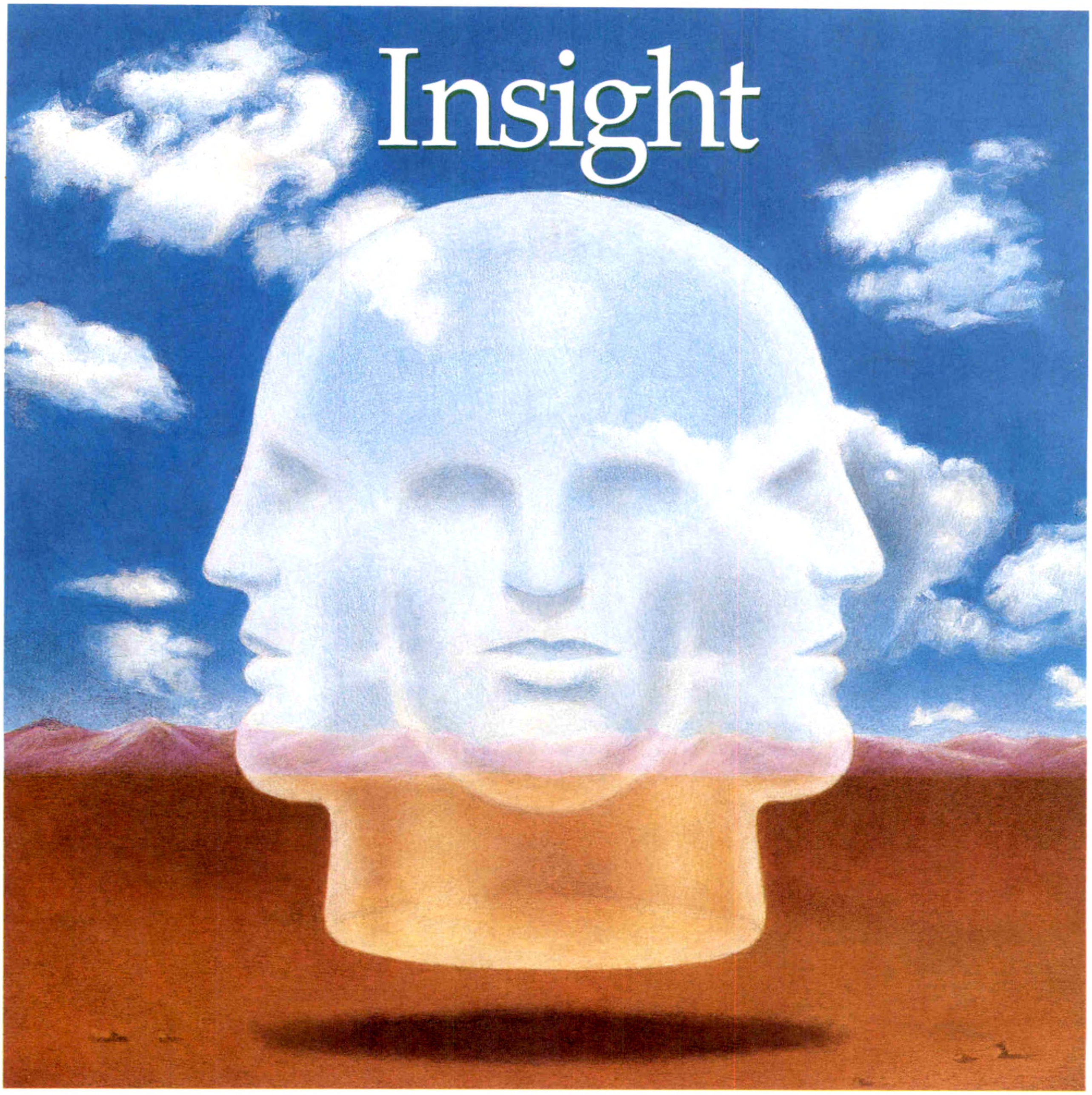

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For the chronic schizophrenic patient, Navane can mean more competent work performance,[1,2] and a smoother path towards social recovery. Navane may help improve the ability to concentrate, and promote a better attitude toward work and co-workers.[1-3]

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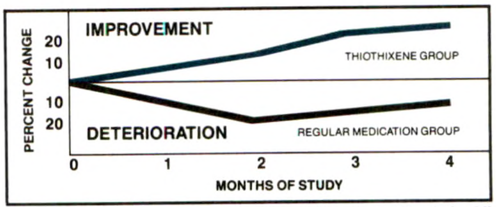

(Adapted from DiMascio and Demirgian[2,3])

Forty-two psychotic male and female patients under age 55 were entered in this study on a nonblind basis, and randomly assigned to their regular medication or switched to thiothixene. Patients were evaluated at baseline and on a daily basis, and periodically rated on the Global Improvement and Brief Psychiatric Rating Scales.

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References: 1. Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. 2. DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. 3. DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. 4. Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry.* Basel, Switzerland, S. Karger, 1969, vol 2, pp 45-52. 5. Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of the American Psychiatric Association, Dallas, May 1-4, 1972. 6. Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Indications: Navane is effective in the management of manifestations of psychotic disorders. Navane has not been evaluated in the management of behavioral complications in patients with mental retardation.

Contraindications: Contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to Information for Patients in the Precautions section, and to the Adverse Reactions section.)

Neuroleptic Malignant Syndrome (NMS)—A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythimas).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane (thiothixene).

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients—Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk. The decision to inform patients and/or their guardians must obviously take into account the clinical circumstances and the competency of the patient to understand the information provided.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. See full prescribing information.

Overdosage: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

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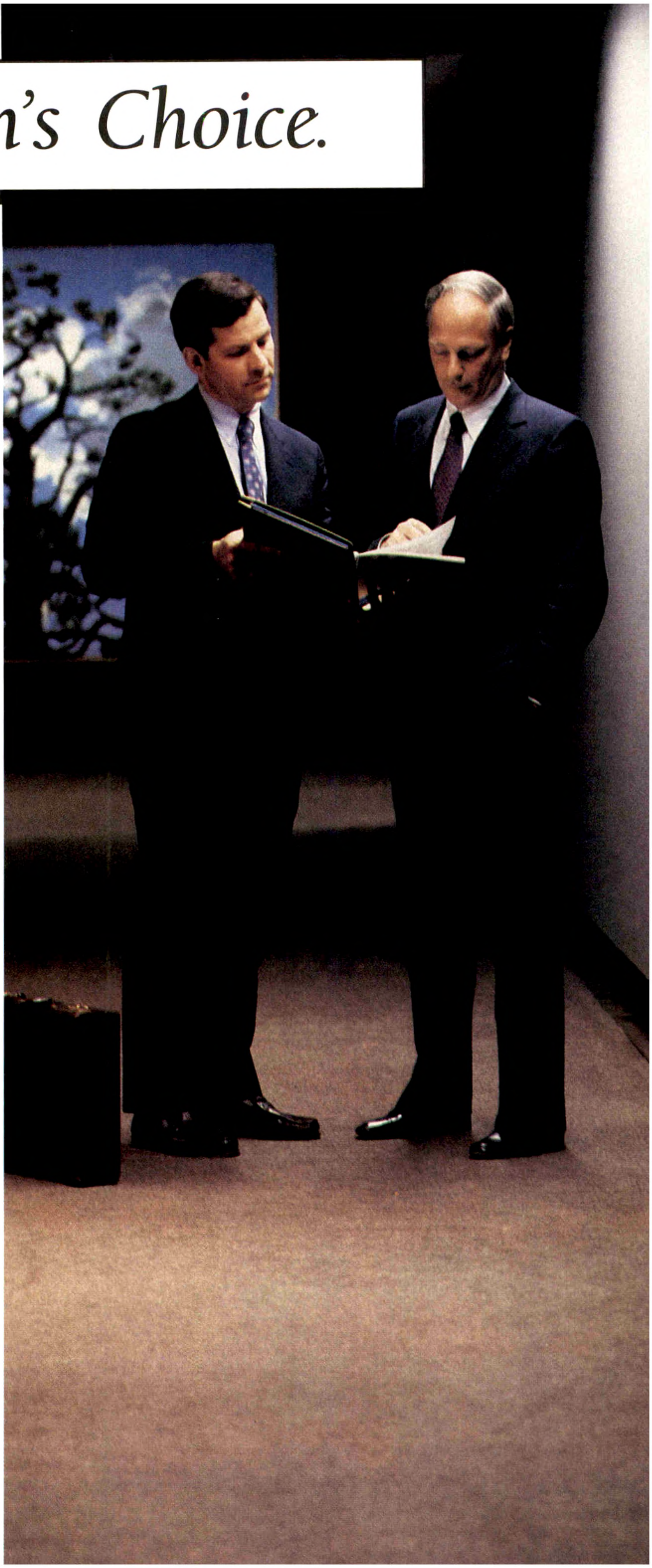

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For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

NOVEMBER

November 3–5, special conference, "Freud: Impact on Twentieth Century Thought," Columbia, South Carolina. Contact Gerry Herron, Division of Psychoanalysis, Department of Neuropsychiatry and Behavioral Science, University of South Carolina, School of Medicine, Columbia, SC 29208; 803-734-7432.

November 5–7, 6th annual conference, The Chronic Patient: Care and Treatment, "The Family: A Crucial Link to Recovery," Jacksonville, Florida. Contact Ed R. Paat, M.S., University Hospital, Community Mental Health Center, 655 West 8th Street, Jacksonville, FL 32209; 904-350-6806.

November 10, special conference, Mount Sinai Hospital, Academic Day VIII presents "Group Psychotherapy for the 1990's," Toronto. Contact M. Leszcz, M.D., F.R.C.P., Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5; 416-586-4567.

November 10–11, special conference, "Suicide Risk in the Elderly: Clinical Assessment and Management," Boston Society for Gerontologic Psychiatry, Boston. Contact Sandra White, 64 Hancock Avenue, Newton, MA 02159; 617-527-5550.

November 10–12, 2nd annual U.S. Psychiatric and Mental Health Congress, New York. Contact Andrea Crossetta, Conference Management Corporation, 200 Connecticut Avenue, Norwalk, CT 06856-4990; 203-852-0500, ext. 226.

November 13–17, International Conference on Rehabilitation Psychiatry, Arusha, Tanzania. Contact Dr. G.P. Kilonzo, Head, Department of Psychiatry, Muhimbili Medical Centre, P.O. Box 65293, Dar Es Salaam, Tanzania.

November 30–December 3, Fall Symposium of the American Back Society, Las Vegas. Contact the American Back Society, 2647 East 14th Street, Suite 401, Oakland, CA 94601; 415-536-9929.

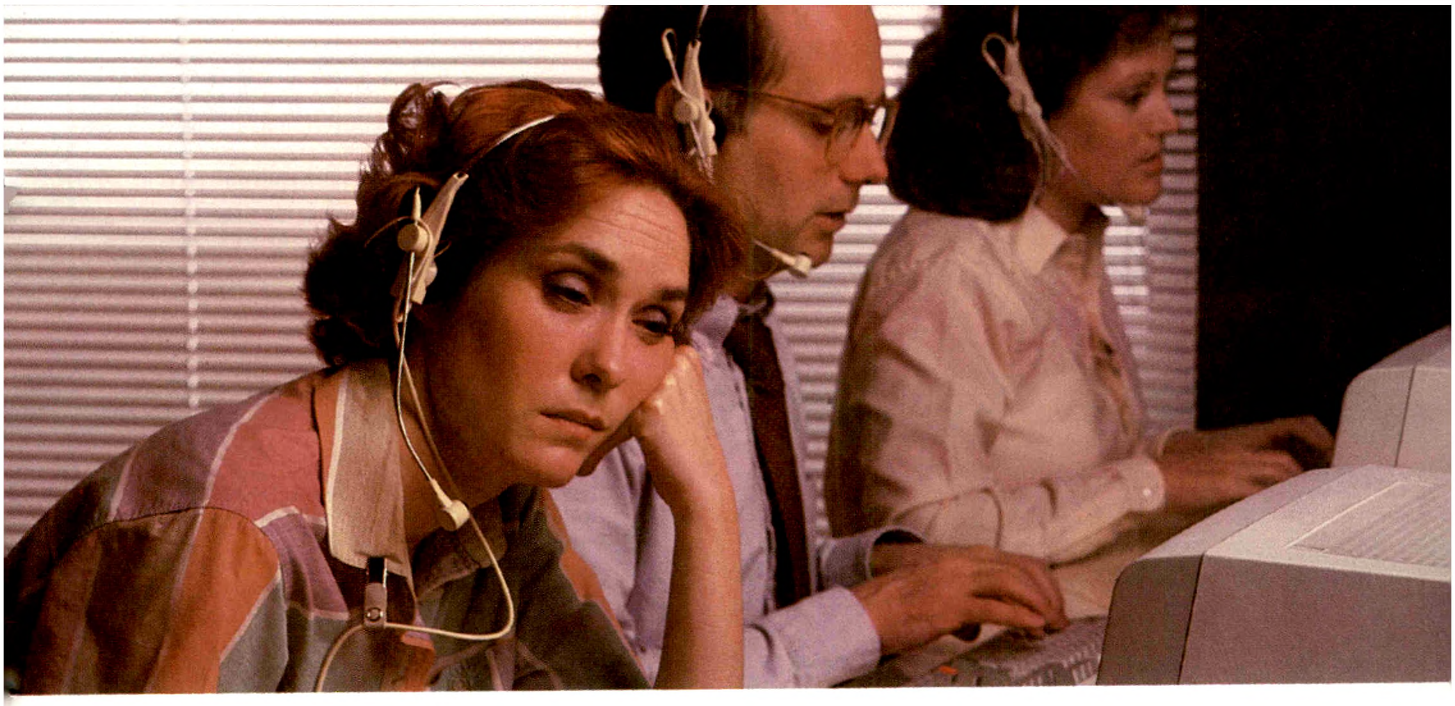
DECEMBER

December 3–6, 6th Annual Northeast Regional Methadone Conference, Newport, Rhode Island. Contact Craig Stenning or Michael Rizzi, 908 Reservoir Avenue, Cranston, Rhode Island 02910; 401-461-5056.

December 5–7, 4th Pan Arab Congress on Psychiatry, Sana'a, Yemen Arab Republic. Contact Dr. Ahmed Mohamed Makki, Congress Secretary, P.O. Box 1390, Sana'a, Yemen Arab Republic; 203304 or 204487.

December 6–8, 9th World Congress of Sexology, Caracas, Venezuela. Contact Organizing Committee, 9th World Congress for Sexology, Apdo. Postal 17302, Caracas 1015A, Venezuela.

December 11–15, International Conference on General Hospital Psychiatry, Cerromar Beach, Puerto Rico. Contact E. Perez, M.D., c/o Joan Bradden, Department of Psychiatry, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario, Canada K1Y 4E9; 613-725-4787.



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Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

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Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage.

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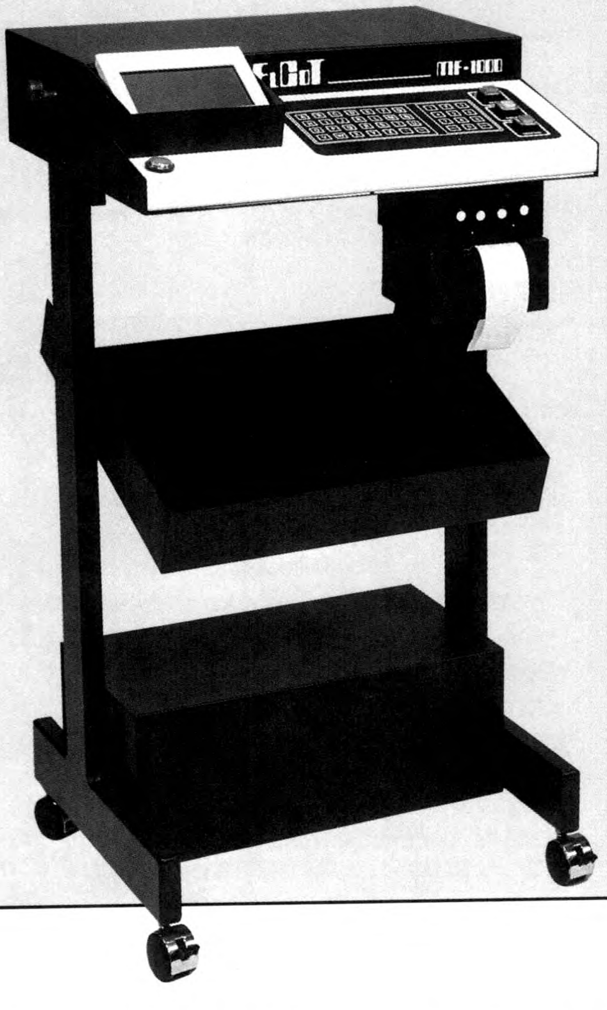

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The Foundation for Advanced Education in the Sciences, Inc. and the National Institute of Mental Health Intramural Research Program present:

PSYCHOPHARMACOLOGY IN PRACTICE

Clinical and Research Update 1989

November 3 and 4, 1989

Washington, D.C.

Organized by:

David Pickar, M.D., Dennis L. Murphy, M.D., Robert M. Post, M.D., William Z. Potter, M.D., Ph.D., and Daniel W. Weinberger, M.D.

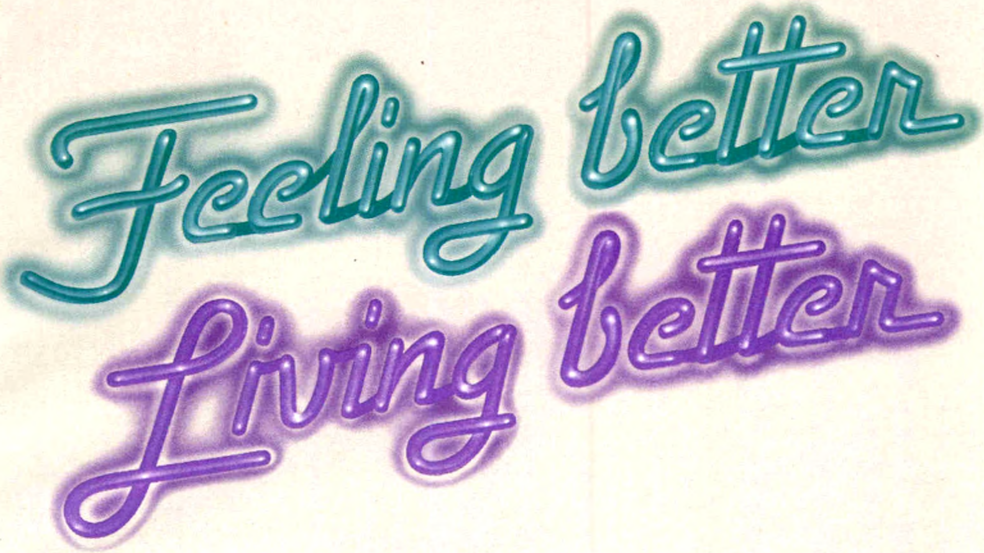
Topics

Neuroanatomic Considerations in Clinical Psychopharmacology
Impact of Brain Imaging on Psychiatric Practice
Advances in the Pharmacotherapy of Schizophrenia
Untoward Effects of Neuroleptic Treatment
Overview of Child Psychiatry
Treatment Approach to the Geriatric Patient
Psychopharmacology of the Borderline Patient
Clinical Genetics in Psychiatry
Treatment of the Refractory Bipolar Patient
Phototherapy and Sleep Deprivation in Affective Illness
Trends in Antidepressant Drug Development
Integrative Approach to the Treatment of Affective Disorders
Neuroimmune and Neuroendocrine Perspectives in Psychiatry
Pharmacotherapeutic Approaches to Alcohol and Drug Abuse

Lectures and panel discussions will focus on the topics outlined above. Tuition for the course is $400 (reduced for residents and fellows). For a course brochure contact **FAES, One Cloister Court, Suite 230, Bethesda, MD 20814-1460 (301-496-7975).**

The FAES/NIH is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The FAES/NIH designates this continuing medical education activity for 16.5 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENTS



NEW Wellbutrin®

(BUPROPION HCl)

helps clear depression with few life-style disruptions.

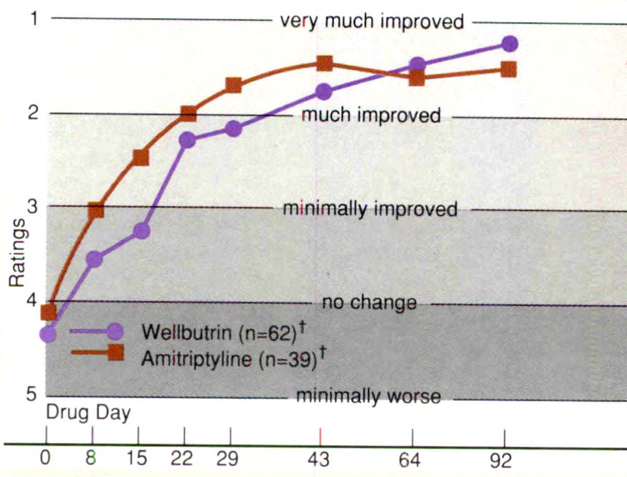
See brief summary of full prescribing information on last pages of this advertisement.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENT

Chemically unique WELLBUTRIN is unrelated to tricyclics/tetracyclics, monoamine oxidase inhibitors, or other known antidepressants.

WELLBUTRIN relieves depression as effectively as amitriptyline.

Clinical Global Improvement*



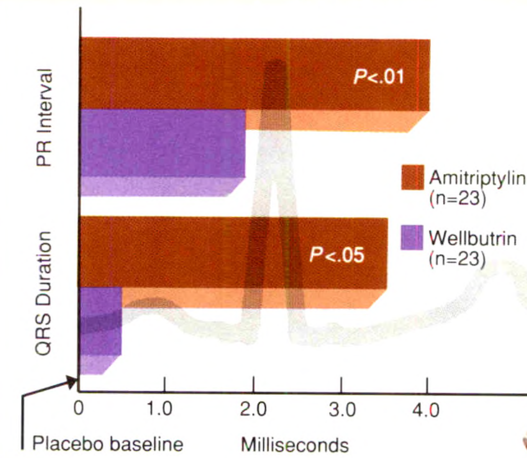
* Adapted from Mendels et al.[1]

† Dosages were 300 to 450 mg/day for WELLBUTRIN, 75 to 150 mg/day for amitriptyline.

Please review IMPORTANT CONSIDERATIONS BEFORE PRESCRIBING WELLBUTRIN on page 6 and brief summary on the last pages of this advertisement before prescribing WELLBUTRIN.

WELLBUTRIN relieves depression with no clinically significant effect on cardiac conduction.

Average Change in EKG Parameters from Baseline Values During Treatment*



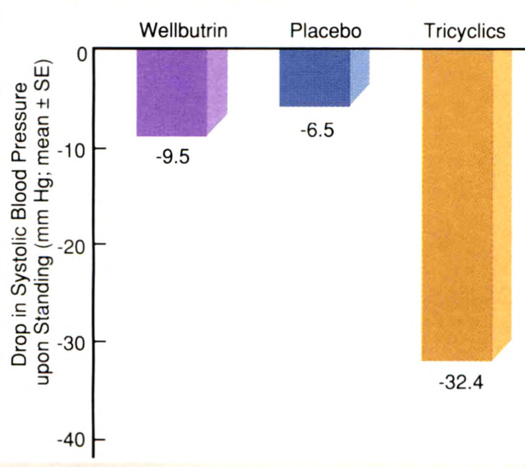
* Adapted from Wenger et al.[2]

"By contrast, the present results with bupropion support the in vitro data demonstrating that this antidepressant lacks these undesirable electro-physiologic properties, and imply that bupropion has a substantially wider margin of safety in man than amitriptyline with regard to cardiac conduction."[2]

Feeling better
Living better

WELLBUTRIN relieves depression with no clinically significant orthostatic hypotension.

Orthostatic Blood Pressure Change (mm Hg)*



* Adapted from Farid et al.[3]

NEW Wellbutrin®
(BUPROPION HCl)

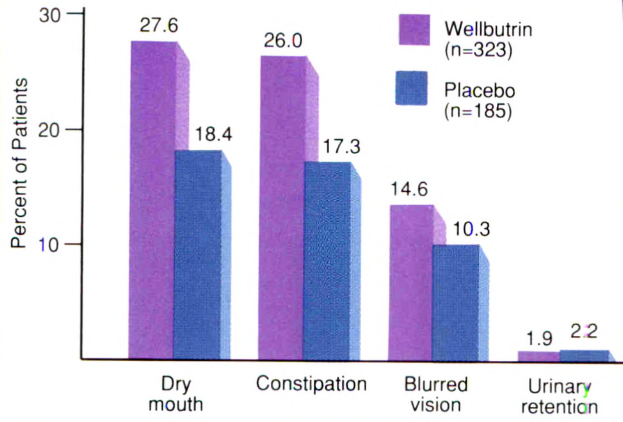
Helping patients to feel better and live better.

See brief summary of full prescribing information

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENT

WELLBUTRIN relieves depression with few anticholinergic side effects.

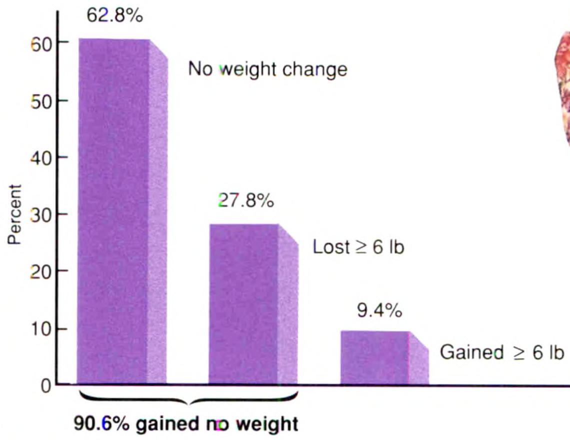
Percent Difference in Anticholinergic Effects Relative to Placebo*



* Data on file, Burroughs Wellcome Co.[4]

WELLBUTRIN relieves depression with little or no weight gain.

Change in Body Weight (percent of patients; n=341)*

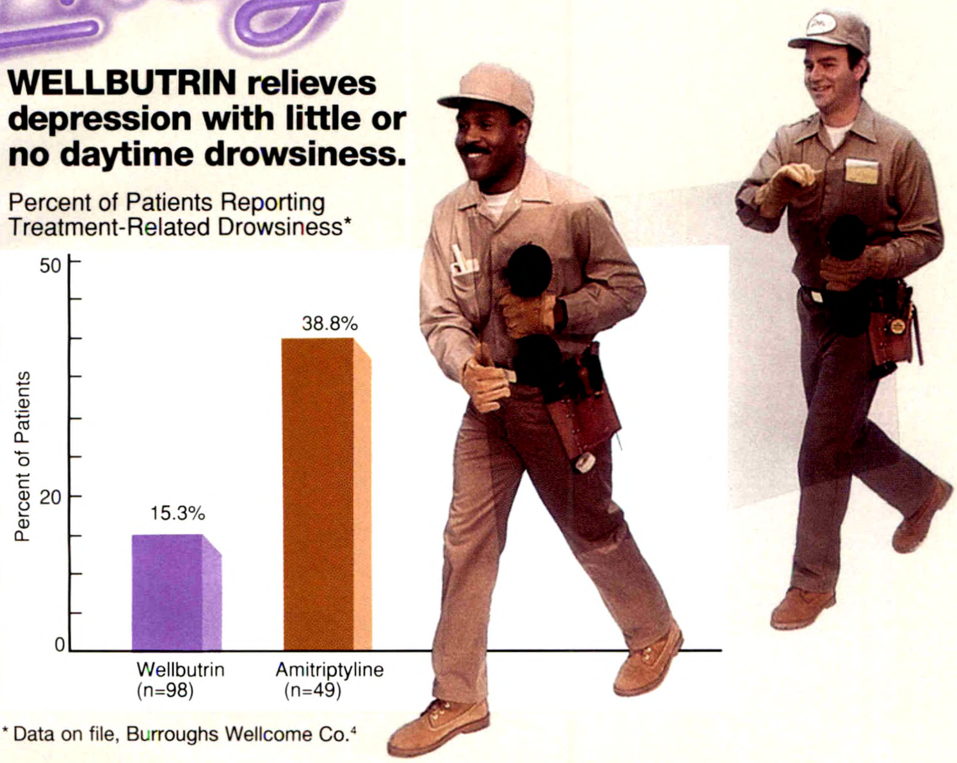


* Data on file, Burroughs Wellcome Co.[4]

Feeling better
Living better

WELLBUTRIN relieves depression with little or no daytime drowsiness.

Percent of Patients Reporting Treatment-Related Drowsiness*



* Data on file, Burroughs Wellcome Co.[4]

In placebo-controlled clinical trials, the incidence of drowsiness* for patients treated with WELLBUTRIN was 19.8%, versus 19.5% for those receiving placebo.

Agitation and Insomnia: A substantial proportion of patients treated with WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of WELLBUTRIN treatment.

**As with all drugs in this category, patients should be cautioned that the ability to perform tasks requiring judgment or motor and cognitive skills may be impaired.*

NEW Wellbutrin®
(BUPROPION HCl)

Helping patients to feel better and live better.

See brief summary of full prescribing information

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIENT

Wellbutrin® (bupropion HCl) helps clear depression with few life-style disruptions.

Important considerations before prescribing Wellbutrin.

Patient Selection Criteria

WELLBUTRIN is contraindicated in patients
- with a seizure disorder
- with a current or prior diagnosis of bulimia or anorexia nervosa
- on monoamine oxidase (MAO) inhibitor therapy
- who are allergic to it

(See CONTRAINDICATIONS section of full prescribing information.)

WELLBUTRIN should be administered with extreme caution to patients
- with a history of seizure, cranial trauma, or other factors that predispose toward seizure
- taking other agents or other treatment regimens that may lower seizure threshold

(See WARNINGS section of full prescribing information.)

Overdosage

In 13 cases of overdose involving WELLBUTRIN, there were no deaths or lasting sequelae.

Seizures

A wide range of seizure rates have been reported with antidepressant therapy with some reports as low as 0.1%. The incidence of seizures with WELLBUTRIN is approximately 0.4%, which may be as much as fourfold higher than some other antidepressants, although no direct comparative studies have been conducted.

Dosage and Administration

The recommended starting dose of WELLBUTRIN is 200 mg/day given as 100 mg b.i.d. Based on clinical response, this dose may be increased to 300 mg/day given as 100 mg t.i.d. no sooner than three days after beginning therapy.

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evenin
1-3	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than 150 mg each, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. Increases in dose should n exceed 100 mg/day in a three-day period. WELLBUTR is available in both 75 mg and 100 mg tablets.

Important: No single dose of WELLBUTRIN should exceed 150 mg because a higher incidence of seizures has been observed in patients receiving higher individual doses of WELLBUTRIN. For this reason, too, patients should be reminded that they should not double up on any dose because they missed a previous one. Dosage should not exceed 450 mg per day (see WARNINGS).

Clinical trials involving more than 7,000 depressed patients and over 200 investigators demonstrated tha **WELLBUTRIN relieves depression in a wide range of patients:**
- with no clinically significant effects on cardiac conduction
- with no clinically significant orthostatic hypotension
- with few anticholinergic side effects
- with little or no weight gain
- with little or no daytime drowsiness

NEW Wellbutri
(BUPROPION HCl)

See brief summary of full prescribing information

WELLBUTRIN® (BUPROPION HYDROCHLORIDE) Tablets

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Wellbutrin is indicated for the treatment of depression. A physician considering the initiation of Wellbutrin should be aware that the drug may cause generalized seizures with an approximate incidence of 0.4% (4/1000). This incidence may exceed that of other antidepressants as much as fourfold. This relative risk is only an approximation since no direct comparative studies have been conducted.

CONTRAINDICATIONS: Wellbutrin is contraindicated in patients: with a seizure disorder; with a current or prior diagnosis of bulimia or anorexia nervosa, because of a higher incidence of seizures noted in such patients; who have shown an allergic response to it; or who are currently being treated with an MAO inhibitor. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Wellbutrin.

WARNINGS:

SEIZURES: Wellbutrin is associated with seizures in approximately 0.4% (4/1000) of patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of other marketed antidepressants by as much as fourfold. This relative risk is only an approximate estimate because no direct comparative studies have been conducted. The estimated seizure incidence for Wellbutrin increases almost tenfold between 450 and 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third the maximum recommended daily dose (450 mg). Given the wide variability among individuals and their capacity to metabolize and eliminate drugs, this disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

During the pre-approval evaluation period, 25 among approximately 2400 patients treated with Wellbutrin experienced seizures. At the time of seizure, 7 patients were receiving daily doses of 450 mg or below, for an incidence of 0.33% (3/1000) within the recommended dose range. Twelve (12) patients experienced seizures at 600 mg per day (2.3% incidence); 6 additional patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

A separate, prospective study was conducted to determine the incidence of seizure during an 8 week treatment exposure in approximately 3200 additional patients who received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond 8 weeks if clinically indicated. Eight (8) seizures occurred during the initial 8 week treatment period and 5 seizures were reported in patients continuing treatment beyond 8 weeks, resulting in a total seizure incidence of 0.4%.

The risk of seizure appears to be strongly associated with dose and the presence of predisposing factors. A significant predisposing factor (e.g., history of head trauma or prior seizure, CNS tumor, concomitant medications that lower seizure threshold, etc.) was present in approximately one-half of the patients experiencing a seizure. Sudden and large increments in dose may contribute to increased risk. While many seizures occurred early in the course of treatment, some seizures did occur after several weeks at fixed dose.

***Recommendations for reducing the risk of seizure:* Retrospective analysis of clinical experience gained during the development of Wellbutrin suggests that the risk of seizure may be minimized if (1) the total daily dose of Wellbutrin does *not* exceed 450 mg, (2) the daily dose is administered t.i.d., with each single dose *not* to exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites, and (3) the rate of incrementation of dose is very gradual. Extreme caution should be used when Wellbutrin is (1) administered to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or (2) prescribed with other agents (e.g., antipsychotics, other antidepressants, etc.) or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine) that lower seizure threshold.**

Potential for Hepatotoxicity: In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. Although scattered abnormalities in liver function tests were detected in patients participating in clinical trials, there is no clinical evidence that bupropion acts as a hepatotoxin in humans.

PRECAUTIONS:

General:

Agitation and Insomnia: A substantial proportion of patients treated with Wellbutrin experience some degree of increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of Wellbutrin treatment.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Patients treated with Wellbutrin have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychotic episodes, confusion, and paranoia. Because of the uncontrolled nature of many studies, it is impossible to provide a precise estimate of the extent of risk imposed by treatment with Wellbutrin. In several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of treatment.

Activation of Psychosis and/or Mania: Antidepressants can precipitate manic episodes in Bipolar Manic Depressive patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Wellbutrin is expected to pose similar risks.

Altered Appetite and Weight: A weight loss of greater than 5 pounds occurred in 28% of Wellbutrin patients. This incidence is approximately double that seen in comparable patients treated with tricyclics or placebo. Furthermore, while 34.5% of patients receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with Wellbutrin did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of Wellbutrin should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for Wellbutrin should be written for the smallest number of tablets consistent with good patient management.

Use in Patients with Systemic Illness: There is no clinical experience establishing the safety of Wellbutrin in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Wellbutrin was well tolerated in patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants.

Because bupropion HCl and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage as bupropion and its metabolites may accumulate in such patients beyond concentrations expected in patients without renal or hepatic impairment. The patient should be closely monitored for possible toxic effects of elevated blood and tissue levels of drug and metabolites.

Information for Patients:

Patients should be instructed to take Wellbutrin in equally divided doses three or four times a day to minimize the risk of seizure.

Patients should be told that any CNS-active drug like Wellbutrin may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that Wellbutrin does not adversely affect their performance they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the use and cessation of use of alcohol may alter the seizure threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible, avoided completely.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Drug Interactions: No systematic data have been collected on the consequences of the concomitant administration of Wellbutrin and other drugs.

However, animal data suggest that Wellbutrin may be an inducer of drug metabolizing enzymes. This may be of potential clinical importance because the blood levels of co-administered drugs may be altered.

Alternatively, because bupropion is extensively metabolized, the co-administration of other drugs may affect its clinical activity. In particular, care should be exercised when administering drugs known to affect hepatic drug metabolizing enzyme systems (e.g., carbamazepine, cimetidine, phenobarbital, phenytoin).

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving concurrent administration of Wellbutrin and L-dopa. Administration of Wellbutrin to patients receiving L-dopa concurrently should be undertaken with caution, using small initial doses and small gradual dose increases.

Concurrent administration of Wellbutrin and agents which lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and small gradual dose increases should be employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a borderline positive response (2-3 times control mutation rate) in some strains in the Ames bacterial mutagenicity test, and a high oral dose (300, but not 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance of these results in estimating the risk of human exposure to therapeutic doses is unknown.

A fertility study was performed in rats; no evidence of impairment of fertility was encountered at oral doses up to 300 mg/kg/day.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: Reproduction studies have been performed in rabbits and rats at doses up to 15-45 times the human daily dose and have revealed no definitive evidence of impaired fertility or harm to the fetus due to bupropion. (In rabbits, a slightly increased incidence of fetal abnormalities was seen in two studies, but there was no increase in any specific abnormality). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: The effect of Wellbutrin on labor and delivery in humans is unknown.

Nursing Mothers: Because of the potential for serious adverse reactions in nursing infants from Wellbutrin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of Wellbutrin in individuals under 18 years old have not been established.

Use in the Elderly: Wellbutrin has not been systematically evaluated in older patients.

ADVERSE REACTIONS: (See also WARNINGS and PRECAUTIONS) Adverse events commonly encountered in patients treated with Wellbutrin are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

Adverse events were sufficiently troublesome to cause discontinuation of Wellbutrin treatment in approximately ten percent of the 2400 patients and volunteers who participated in the product's pre-approval clinical trials. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

NOW AVAILABLE FOR DEPRESSION IN A WIDE RANGE OF PATIEN

The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Wellbutrin under relatively similar conditions of daily dosage (300-600 mg), setting, and duration (3-4 weeks). The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors must differ from those which prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of Wellbutrin is provided in the WARNINGS and PRECAUTIONS sections.

TREATMENT EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Wellbutrin Patients (n = 323)	Placebo Patients (n = 185)
CARDIOVASCULAR		
Cardiac Arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
DERMATOLOGIC		
Pruritus	2.2	0.0
Rash	8.0	6.5
GASTROINTESTINAL		
Anorexia	18.3	18.4
Appetite Increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/Vomiting	22.9	18.9
Weight Gain	13.6	22.7
Weight Loss	23.2	23.2
GENITOURINARY		
Impotence	3.4	3.1
Menstrual Complaints	4.7	1.1
Urinary Frequency	2.5	2.2
Urinary Retention	1.9	2.2
MUSCULOSKELETAL		
Arthritis	3.1	2.7
NEUROLOGICAL		
Akathisia	1.5	1.1
Akinesia/Bradykinesia	8.0	8.6
Cutaneous Temperature Disturbance	1.9	1.6
Dry Mouth	27.6	18.4
Excessive Sweating	22.3	14.6
Headache/Migraine	25.7	22.2
Impaired Sleep Quality	4.0	1.6
Increased Salivary Flow	3.4	3.8
Insomnia	18.6	15.7
Muscle Spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory Disturbance	4.0	3.2
Tremor	21.1	7.6
NEUROPSYCHIATRIC		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased Libido	3.1	1.6
Delusions	1.2	1.1
Disturbed Concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
NONSPECIFIC		
Fatigue	5.0	8.6
Fever/Chills	1.2	0.5
RESPIRATORY		
Upper Respiratory Complaints	5.0	11.4
SPECIAL SENSES		
Auditory Disturbance	5.3	3.2
Blurred Vision	14.6	10.3
Gustatory Disturbance	3.1	1.1

*Events reported by at least 1% of Wellbutrin patients are included.

Other events observed during the entire pre-approval evaluation of Wellbutrin: During its pre-approval assessment, Wellbutrin was evaluated in almost 2400 subjects. The conditions and duration of exposure to Wellbutrin varied greatly and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by Wellbutrin. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections of the labeling.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular: Frequent was edema; infrequent were chest pain, EKG abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; and rare were pallor and phlebitis.

Dermatologic: Frequent were nonspecific rashes; infrequent were alopecia and dry skin; rare were change in hair color and hirsutism.

Endocrine: Infrequent was gynecomastia; rare were glycosuria and hormone level change.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare were rectal complaints, colitis, G.I. bleeding, and intestinal perforation.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis, urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and painful ejaculation.

Hematologic/Oncologic: Rare was lymphadenopathy.

Neurological: (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; and rare were EEG abnormality, abnormal neurological exam, impaired attention, and sciatica.

Neuropsychiatric: (see PRECAUTIONS) Frequent were mania/hypomania, increased libic
hallucinations, decrease in sexual function, and depression; infrequent were memory ir
pairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, forr
thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum i
ritation, and oral edema; rare was glossitis.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare were epista
and rate or rhythm disorder.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare we
body odor, surgically related pain, infection, medication reaction and overdose.

Post-Approval Reports: The following additional events were rarely observed (less th
1/1000 patients) post-approval.

Cardiovascular: Flushing and myocardial infarction.

Dermatologic: Acne.

Gastrointestinal: Stomach ulcer.

Hematologic/Oncologic: Anemia and pancytopenia.

Neurological: Aphasia.

Musculoskeletal: Musculoskeletal chest pain.

Respiratory: Pneumonia and pulmonary embolism.

OVERDOSAGE:

Human overdose experience: There has been limited clinical experience with overdosa
of Wellbutrin. Thirteen overdoses occurred during clinical trials. Twelve patients ingeste
850 to 4200 mg and recovered without significant sequelae. Another patient who ingeste
9000 mg of Wellbutrin and 300 mg of tranylcypromine experienced a grand mal seizu
and recovered without further sequelae.

DOSAGE AND ADMINISTRATION:

General Dosing Considerations: It is particularly important to administer Wellbutrin in a ma
ner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose shou
not exceed 100 mg/day in a 3 day period. Gradual escalation in dosage is also importa
if agitation, motor restlessness, and insomnia, often seen during the initial days of trea
ment, are to be minimized. If necessary, these effects may be managed by temporary redu
tion of dose or the short-term administration of an intermediate to long-acting sedative hy
notic. A sedative hypnotic usually is not required beyond the first week of treatment. I
somnia may also be minimized by avoiding bedtime doses. If distressing, untoward effec
supervene, dose escalation should be stopped.

No single dose of Wellbutrin should exceed 150 mg. Wellbutrin should be administered t.i.d
preferably with at least 6 hours between successive doses.

Usual Dosage for Adults: The usual adult dose is 300 mg/day, given t.i.d. Dosing shou
begin at 200 mg/day, given as 100 mg b.i.d. Based on clinical response, this dose m
be increased to 300 mg/day, given as 100 mg t.i.d., no sooner than 3 days after beginnin
therapy (see table below).

Dosing Regimen

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evenin
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

Increasing the Dosage Above 300 mg/Day: As with other antidepressants, the full a
tidepressant effect of Wellbutrin may not be evident until 4 weeks of treatment or longe
An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not mo
than 150 mg each, may be considered for patients in whom no clinical improvement is note
after several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be a
complished using the 75 or 100 mg tablets. The 100 mg tablet must be administered q.i.
with at least 4 hours between successive doses, in order not to exceed the limit of 150 m
in a single dose. Wellbutrin should be discontinued in patients who do not demonstrate a
adequate response after an appropriate period of treatment at 450 mg/day.

Elderly Patients: In general, older patients are known to metabolize drugs more slowly a
to be more sensitive to the anticholinergic, sedative, and cardiovascular side effects of a
tidepressant drugs.

References: **1.** Mendels J, Amin MM, Chouinard G, et al.
A comparative study of bupropion and amitriptyline in depressed
outpatients. *J Clin Psychiatry.* 1983;44(5, sec 2):118-120. **2.** Wen
TL, Cohn JB, Bustrack J. Comparison of the effects of bupropion
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Contraindications: Comatose states or presence of large amounts of C.N.S. depressants.

Warnings: The possibility of extrapyramidal reactions from chlorpromazine may confuse the diagnosis of Reye's syndrome or other encephalopathy. Therefore, avoid use in children or adolescents with suspected Reye's syndrome.

May cause persistent tardive dyskinesia, which appears to be irreversible in some patients. Reserve chronic neuroleptic treatment for patients with chronic illness 1) that is known to respond to neuroleptics and 2) for whom there are no safer but equally effective treatment options. Use the smallest effective dose over the shortest treatment duration. If signs and symptoms of tardive dyskinesia develop, consider discontinuing the neuroleptic. A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. To manage NMS 1) discontinue immediately antipsychotic drugs and any other drugs not essential to concurrent therapy; 2) treat symptoms intensively and monitor; 3) where possible, treat serious concomitant medical problems. If antipsychotic treatment is needed after recovery from NMS, consider reintroducing drug therapy and monitor the patient carefully as recurrences of NMS have been reported. 'Thorazine' ampuls and vials contain sodium bisulfite and sodium sulfite; the sulfite may cause allergic reactions, including anaphylactic symptoms. In patients with bone marrow depression or previously demonstrated hypersensitivity (e.g., blood dyscrasias, jaundice) with phenothiazines, do not administer 'Thorazine' unless the potential treatment benefits outweigh the possible hazards. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days therapy. Avoid concomitant use with alcohol. May counteract antihypertensive effect of guanethidine and related compounds. Use in pregnancy only when essential. There are reported instances of prolonged jaundice, extrapyramidal signs, hyperreflexia or hyporeflexia in newborns whose mothers had received chlorpromazine. Chlorpromazine is excreted in the breast milk of nursing mothers.

Precautions: Advise patients and/or guardians of the risk of tardive dyskinesia from chronic therapy. Use cautiously in persons with cardiovascular, liver or chronic respiratory disease, or with acute respiratory infections. Patients with a history of hepatic encephalopathy due to cirrhosis have increased sensitivity to the C.N.S. effects of chlorpromazine. Due to cough reflex suppression, aspiration of vomitus is possible. May prolong or intensify the action of C.N.S. depressants, organophosphorus insecticides, heat, atropine and related drugs. (Reduce dosage of concomitant C.N.S. depressants.) Anticonvulsant action of barbiturates is not intensified.

Neuroleptic drugs cause elevated prolactin levels that persist during chronic administration. Since approximately one-third of human breast cancers are prolactin-dependent *in vitro*, this elevation is of potential importance if neuroleptic drug administration is contemplated in a patient with a previously detected breast cancer. Neither clinical nor epidemiologic studies to date, however, have shown an association between the chronic administration of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in glaucoma patients. May diminish the effect of oral anticoagulants, produce α-adrenergic blockade, and lower the convulsive threshold; dosage adjustment of anticonvulsants may be required. May interfere with Dilantin®* metabolism, causing 'Dilantin' toxicity. May cause false positive phenylketonuria test results. Do not use with Amipaque®†. Discontinue 'Thorazine' at least 48 hours before myelography, do not resume for at least 24 hours postprocedure, and do not use to control N/V prior to myelography or postprocedure with 'Amipaque'. Evaluate patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics periodically to decide whether the dosage could be reduced or therapy discontinued. Antiemetic effect may mask signs of overdosage of other drugs or obscure diagnosis and treatment of conditions such as intestinal obstruction, brain tumor and Reye's syndrome (see Warnings). When used concomitantly, may obscure vomiting as a sign of toxicity of a cancer chemotherapeutic agent. Discontinue high-dose, long-term therapy gradually. Patients with a history of long-term therapy with 'Thorazine' and/or other neuroleptics should be evaluated periodically for possible adjustment or discontinuance of drug therapy.

Adverse Reactions: Drowsiness; cholestatic jaundice; agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, aplastic anemia, thrombocytopenic purpura and pancytopenia; postural hypotension, tachycardia, fainting, dizziness and occasionally a shock-like condition; reversal of epinephrine effects; EKG changes have been reported; neuromuscular (extrapyramidal) reactions: dystonias, motor restlessness, pseudo-parkinsonism, persistent tardive dyskinesia, psychotic symptoms, catatonic-like states, cerebral edema; convulsive seizures; abnormality of the cerebrospinal fluid proteins; urticarial reactions and photosensitivity, exfoliative dermatitis, contact dermatitis; asthma, laryngeal edema, angioneurotic edema, and anaphylactoid reactions; lactation and breast engorgement (in females on large doses), false positive pregnancy tests, amenorrhea, gynecomastia; hyperglycemia, hypoglycemia, glycosuria; dry mouth, nasal congestion, constipation, adynamic ileus, urinary retention, priapism, miosis, mydriasis; after prolonged substantial doses, skin pigmentation, epithelial keratopathy, lenticular and corneal deposits and pigmentary retinopathy, visual impairment; mild fever (after large I.M. doses); hyperpyrexia; increased appetite and weight; a systemic lupus erythematosus-like syndrome; peripheral edema.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported but no causal relationship has been established.

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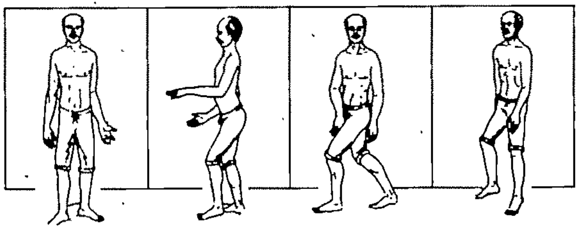

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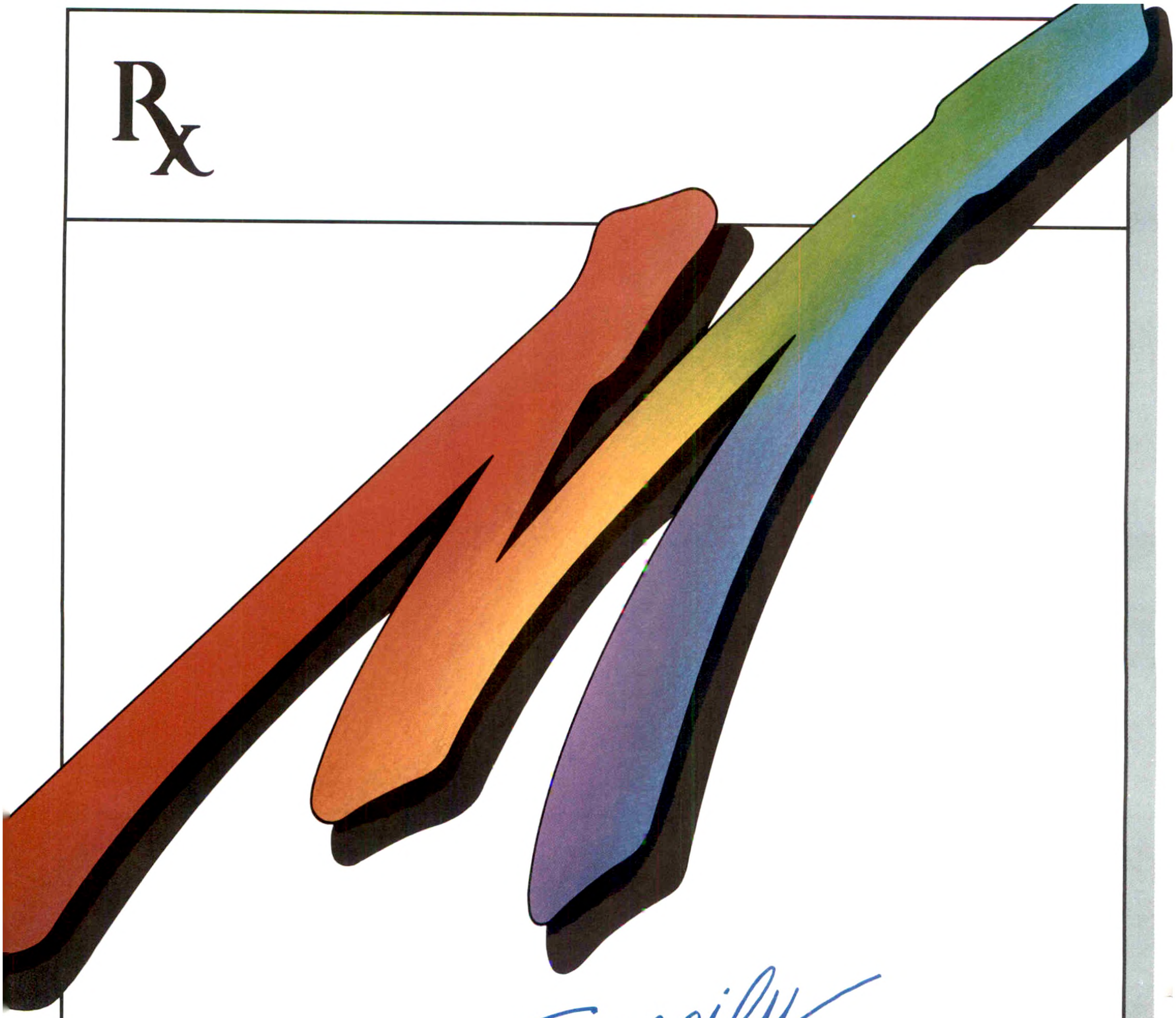

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The *Journal's* New Deputy Editor

Unless it be the section entitled "Information for Contributors," no part of a scientific journal is less frequently read than its masthead. The deepest and darkest of secrets is safe in these editorial penetralia and remains undisclosed in the obscurity of print. It is for that reason that we wish to draw the attention of the *Journal's* readers to a change appearing in the masthead of this issue that betokens an important event in the *Journal's* editorial life—the appointment of Dr. Nancy C. Andreasen to the position of Deputy Editor.

Dr. Andreasen is no stranger to the *Journal.* For a number of years she was an assiduous reviewer of manuscripts—a devotion to scholarship that led to her being asked to join the Editorial Board in 1979. A year later she was appointed Editor of the *Book Forum*, a position she continued to hold after completing two four-year terms as Associate Editor in 1987 and filled with a degree of distinction and imagination that has made that section of the *Journal* the favorite of many of our readers.

As the official publication of an Association whose membership has a wide diversity of interests and talents, the *Journal* must be representative of the many different paths up the mountain of psychiatric and scientific truth. Dr. Andreasen's appointment will ensure the continuance of that editorial principle. She brings to her new post an extensive knowledge of the neurobiological basis of mental disorders, with a special emphasis on the pathological states of the brain in patients with schizophrenia and the delineation of those states by the techniques of brain imaging. As Deputy Editor she will be able to apply that knowledge to the selection of biological papers for publication in the *Journal's* pages, and, in particular, she will be in a position increasingly to focus the *Journal's* critical attention on the rapidly growing understanding of CNS pathophysiology and its correlation with psychological dysfunction.

We must take note, however, of the fact that Dr. Andreasen's interests and sensibilities go beyond the confines of biological psychiatry. Anyone who has read the *Book Forum* in recent years is familiar with the rich variety of topics covered in the reviews published in that section. This has been by design, not by chance, and reflects Dr. Andreasen's awareness of the importance of the humanistic as well as the more narrowly scientific understanding of human nature. This will come as no surprise to anyone familiar with Dr. Andreasen's academic background. Not only did she begin her professional life as a student of English literature, but the first three or four of her nearly 200 published books and articles are devoted to the work and significance of the poet John Donne. As they join us in warmly welcoming Dr. Andreasen to her new duties, our readers may rest assured that, whether their predilection is for "mandrake root" or for "envy's stinging," the *Journal* will strive to meet their varied needs.

J.C.N.

Psychiatric Services in Jails and Prisons: Who Cares?

On any day, our nation's jails and prisons hold an estimated 1.2 million men and women. Many studies have consistently demonstrated that about 20% of these inmates are seriously mentally ill and in need of psychiatric care. Up to 5% are actively psychotic. What constitutes psychiatric care for these people? Who will care for these people? Who cares?

In the Official Actions section of this issue of the *Journal* is a position statement developed by the APA Task Force on Psychiatric Services in Jails and Prisons and approved by the Assembly of District Branches and the Board of Trustees. It reaffirms that "the American Psychiatric Association accords a high priority to the care and treatment of patients from groups that are underserved, especially groups that lack strong political constituencies. Such groups include the chronically mentally ill and the mentally ill homeless. Also included, but less visible, are the mentally ill in jails and prisons."

This position statement traces APA's concern for the mentally ill in jails and prisons over the past two decades, rejecting an "out of sight, out of mind" mentality and the unstated dynamic that medical and psychiatric neglect should be a part of the criminal justice process of retribution and punishment.

And yet, in what many regard as difficult days for psychiatry, these issues are far from the active concerns of the average psychiatric practitioner. This is understandable, but what about the responsibility of the profession? What about our ideals of public service?

On the other hand, in these often problematic settings, where almost all of psychiatry's problems are raised to a higher power, is the attempt to bring quality psychiatric care to these patients a cruel joke? Where serious political and economic problems are the rule (such as harsh questions of the allocation of very scarce resources and grossly inadequate remuneration), is this the time or the place for "pie in the sky"?

Then, of course, there are the subtle (and sometimes not so subtle) ethical conflicts: informed consent in these settings, confidentiality (are you kidding?), and divided loyalties, not to mention the unexamined countertransference. Is it any wonder that some may say, "Who needs it?"

Well, we need it. In a time of profound internal professional questioning and external competition, what better way to adopt an active leadership stance and develop and maintain the highest standards of practice? What better test of our goal of bringing quality care to the needy? What better challenge to our ideals, our resolve? What better way to play a major part in reforming this neglected aspect of our health and mental health care delivery system?

The position statement sets out a number of principles:

1. The fundamental goal of a mental health service should be to provide the same level of care to patients in the criminal justice process that is available in the community.
2. The effective delivery of mental health services in correctional settings requires that there be a balance between security and treatment needs. There is no inherent conflict between security and treatment.
3. A therapeutic environment can be created in a jail or a prison setting if there is clinical leadership, with authority to create such an environment.
4. Timely and effective access to mental health treatment is a hallmark of adequate mental health care. Necessary staffing levels should be determined by what is essential to ensure that access.
5. Psychiatrists should take a leadership role administratively as well as clinically. Further, it is imperative that psychiatrists define their professional responsibilities to include advocacy for improving mental health service in jails and prisons.

The specific objectives that are required to meet these goals are set out in the report of the task force, which also has been recently approved by the Board of

Trustees. This document is made up of two parts. The first part, "Principles Governing the Delivery of Psychiatric Services in Jails and Prisons," deals with such issues as the quality of care, confidentiality, informed consent, research, and treatment as well as administration and administrative issues, education and training, and interprofessional relationships. It calls for more training in correctional psychiatry at the residency level and increased efforts by academic departments to reach out to correctional facilities in order to establish affiliations for the provision of services, education, and research.

The second part of the task force report, "Guidelines for Psychiatric Services in Jails and Prisons," provides specific standards for the delivery of essential psychiatric services in the three major types of facilities: lockups, jails, and prisons. For each type of facility, services are grouped under four categories: screening and evaluation, crisis intervention, treatment, and discharge/transfer planning. The latter section responds to the fact that efforts to develop community resources to support the reintegration of a mentally ill population back into society are even more pervasively problematical in correctional psychiatry than they are in public psychiatry in general.

Finally, it is important to note that these principles and guidelines supplement the standards set out by the National Commission on Correctional Health Care. This commission, which grew out of an American Medical Association-sponsored consortium of national health care organizations, including APA, whose members provide health care services in jails and prisons, has developed an excellent set of standards and a highly regarded accreditation process. That the APA guidelines are thus based on and complementary to American Medical Association-derived standards of practice is consistent with the remedicalization of psychiatry.

APA's "Position Statement on Psychiatric Services in Jails and Prisons" is, most of all, a call to action: a call for the participation of the members of APA in this important public service. By adopting this position statement and the principles and guidelines for psychiatric services in jails and prisons, APA emphatically asserts that it cares and that psychiatrists should and will in the future be a substantial presence in these settings.

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Paul J. Fink, M.D.

Presidential Address: On Being Ethical in an Unethical World

Paul J. Fink, M.D.

In a recent issue of the *Journal of the American Medical Association*, a column entitled "Belinda, Asleep Without Dreams," carefully detailed the story of a child comatose from having been severely beaten. The author, Dr. Kris Sperry, wrote the following:

> In the wink of an eye, an emotional outburst killed a small child, and coincidentally shattered two families just as surely as this little one's skull had been broken into jagged pieces. Guilt, recrimination, regret, and hate suddenly became paramount, fueled by suspicion. Normally placid day-to-day family activities were invaded by the legal, police, and social welfare systems, all attempting to achieve some understanding of an event that is inherently impossible to understand.
>
> As I drove home that evening [the author continued], questions raged in my thoughts: "Why do we continue to kill and maim our children? What actions of a 13-month-old child are so heinous that smashing her head against the floor is the only recourse? What punishment could be meted out to the perpetrator, in the name of justice, that will even begin to replace the beauty of a single smile from this dead child? When will I never see another dead or dying baby, mortally hurt at the hands of those whom it unwaveringly loves and trusts?" My heart ached, and my eyes misted over with tears of rage, frustration, and sorrow. (1)

Sloan et al. (2) have discussed the difference in the use of guns in two cities, Seattle and Vancouver. In one city there is strict handgun regulation; in the other there is not. The authors clearly showed that while violence may be the same in both places, the use and availability of guns make one city considerably more dangerous than the other. It is interesting that this article, appearing in a major medical journal, deals with a public health issue that is as much sociological as it is medical, if not more so.

The *Journal of the American Medical Association* reports that interpersonal violence is the second leading cause of death for all 15- to 24-year-olds and the fourth leading cause of potential years of life lost. In 1980, it accounted for 350,000 hospitalizations and 1.5 million hospital days and for $640 million in health care costs (3).

Gerbner's research on light versus heavy television viewers provides important evidence of lack of trust in the community. He and his colleagues compared the two groups and found that heavy television viewers, who were treated to an enormous amount of violence during prime time, including 80 murders a week in addition to endless cruelty, manipulation, violation, and physical harm to person and damage to property, were more frightened, expected to be robbed, were more suspicious, and more inured to violence in the community.

Although the media often exaggerate trends, often convey distortions through stereotypes, and often fail to balance the evil with the good, they do describe the violent and fearful world we live in. On March 25, 1989, the *New York Times* (4) ran an article whose headline read "Parents in Terror: Could My Child Be My Killer?" The story told of parents who are terrified and terrorized by their children and described vicious battering, financial theft, sexual assault, and a man killing his blind father's guide dog so as to make the older man completely dependent upon him. The idea that "blood is thicker than water" is clearly diminished, if not erased, by a vivid and rapid change in values and morality that allows this kind of incident to

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be more than the exception; fortunately, however, it is not yet the rule.

Violence is escalating, fear is escalating, and the entire nature and tone of our social fabric are changing more rapidly and with greater sinister meaning than ever before in the last century. During my tenure as President of our organization I have had the opportunity to travel widely and have been deeply impressed by the different social contexts in which medicine and psychiatry are practiced around the country and around the world. Today I will talk about the changes in the social fabric, that is, the problems of ethical collapse facing the larger world and the implications of these changes for the ethical practice of psychiatry; next I will discuss the role of fiscal *changes related to these problems*; and finally I will make several suggestions for steps we must take toward a recommitment to ethics and compassion in our field.

CHANGING ATTITUDES AMONG PHYSICIANS

The complexity of these issues should not be mitigated by an attempt to be glib or an effort to find quick and easy explanations. Professional ethics can only be reevaluated in the context of the value systems of the society and of the extraordinary tolerance for violent and destructive acts that shapes the sensitivities and sensibilities of our citizens. Every physician is also a citizen in this social context, as well as a developing child and adult long before he or she enters medical school to take on the mantle of physicianhood and the ethical structure of the profession.

Petersdorf captured my meaning and concern in a recent paper that deals with ethical problems in medical education and research. He reported on an interesting study that

> sampled the attitudes of medical students towards physician fraud and abuse in the Medicare and Medicaid programs. Fraud was exemplified by billing for services that were not performed, while abuses consisted mostly of overutilization, such as performing unnecessary lab tests or sending patients from one specialist to another. The students' attitudes towards these practices were remarkably lenient. Most thought fraud and abuse would go unpunished or at worst would be penalized by a warning, a fine, or temporary suspension from the Medicare and/or Medicaid program. Many excused the physicians because the programs reimbursed at such low rates and took so long to do so. Few thought in terms of delicensing, criminal probation, or incarceration. One has to wonder whether such forgiveness of the misdeeds of practicing physicians was not engendered during acculturation in college, medical school, and housestaff training, and whether it is not likely to encourage laxity with respect to research fraud and misconduct among these students when they become basic scientists and clinical investigators. (5)

Further, each of those persons was a physician before he or she moved to reshape his or her thinking, ethics, and values to become a psychiatrist. Thus, we cannot consider the ethical standards of psychiatry without understanding the changes in the ethical framework of the practice of medicine, and we cannot understand the issues of medical ethics without placing them in the contexts of a rapidly changing social fabric, ethics, and the fluidity of morality at this moment in history.

As a science, psychiatry has made inroads in the understanding of psychosexual development in children and adolescent and adult development. We have learned about superego development and conscience, but relatively little attention has been devoted to those larger social forces that buttress and define these developmental milestones. We know a great deal about the development of character and personality but relatively little about the distortions wrought by social consensus on the shifting and changing ethical standards by which we live. We know even less about how these social factors affect our development as medical practitioners, specifically, how are we to develop ethical standards as clinicians in an increasingly unethical world?

THE PROBLEM OF PROFESSIONAL ETHICS

Webster's Ninth New Collegiate Dictionary defines morals, values, and ethics as follows:

> *morals* 1 a: of or relating to principles of right and wrong in behavior b: expressing or teaching a conception of right behavior . . . MORAL implies conformity to established sanctioned codes or accepted notions of right and wrong
> *values* 7: something (as a principle or quality) intrinsically valuable or desirable
> *ethics* 1 a: a system of moral principles b: the rules of conduct recognized in respect to a particular class of human actions of a particular group or culture.

In using the dictionary definitions of morals, values, and ethics, it is difficult to distinguish among these three ideas or terms and to see them as separate forces in our lives. They are so intertwined that most people use the terms interchangeably. My own definitions are simpler but are similar. Morals are universal rules such as the Ten Commandments, values are learned attitudes, and professional ethics are guidelines of behavior for a profession. Lowy put it beautifully:

> The difficulty of defining appropriate professional rules and establishing boundaries to expertise and obligation is greater for psychiatry than for other medical disciplines. Likewise, the social control functions of psychiatrists, while not unique, are more extensive than those thrust upon other physicians. Finally, the objectives of psychiatry are not so clear operationally as those of medicine generally (preservation of life, relief of suffering, prevention of disease, promotion of health) because of the ambiguity and disagreement regarding what constitutes mental health, normality, and mental illness. The psychiatrist may well make decisions that, both ethically and technically,

> are heavily influenced by the socio-cultural context, the psychiatrist's personal beliefs and value systems, loyalties to institutions or ideals, etc. However, these influences may be unrecognized and/or unacknowledged and treatment or advice may be presented as though technical medical considerations alone are operative. Further, in pluralistic societies consensus regarding what is right and good is often difficult. (unpublished paper, 1989)

Two examples may help to clarify the concern that I have about the society which produces the current and future doctors, determines their values and morals, and ultimately determines their willingness to adhere to professional ethics. First, the question of heroes and antiheroes. Heroes are consensually validated representations of particular values and social ideals. Our choice of heroes reflects something about the morality of our nation. A survey of American campuses found that Clint Eastwood was the most popular and most important hero among American students; second was Sylvester Stallone. Not the President, not the Chief Justice, not the winner of the Nobel Prize for medicine or physics, but two actors whose claim to fame is the enactment of wanton murder and the exaltation of indiscriminate violence.

MONEY AND ITS RELATION TO ETHICS

This nation has escalated the antihero beyond heroic proportions. J.R. Ewing was an ugly hero. The nation's toleration of sleaze in government and the widespread cheating in universities indicate that immorality is everywhere. Institutions such as the church and the family, which formerly set the standards of moral behavior and sound values, have been seriously weakened. The following story is a good example. In a public broadcasting system documentary on the view that Americans have of big business, Eli Wallach, the host of the show, demonstrated that most Americans think of the chief executive officers of the Fortune 500 as crooks, each of whom would be willing to kill to ensure a successful deal. Wallach then asked a tenth-grade class, "How much money would it take for you to kill somebody in order to have a successful business deal?" Incredibly, only one student answered that no amount of money would induce him to kill another person. The fabric of American life is interwoven with the business world and the concept of the successful entrepreneur millionaire who has all the finery and acquisitions through which to create a personal identity and a value system that is not unlike the acquisitiveness that Christopher Lasch described in his book *The Culture of Narcissism* (6).

Burchell et al. described the evolution of medicine's economic structure as follows:

> it includes complex organizations as well as increasing sophistication of existing organizations. The result is an environment in which the governance, organization design, goals, policies, professional staffing, products and services, target markets, and related factors that make up organizations undergo alteration. The evolution of medicine's economic structure is also characterized by several trends:
>
> 1. Investor-owned health care organizations, which produce large medical care delivery systems, are growing. Control is pursued by professional managers who are responsible for balancing often conflicting goals (eg, quality of care, low organizational costs, high patient satisfaction, high provider productivity).
> 2. Multi-institutional alliances, arrangements, and systems that intensify the organizational complexity surrounding medical practice are proliferating.
> 3. Profitability is now openly recognized as a legitimate goal for providers and organizations. Profit, productivity, and efficiency are attaining equity with quality-of-care goals in the provision of medical care.
> 4. Not-for-profit health care organizations are changing into for-profit corporations, and nonprofit entities are forming alliances with for-profit entities as a means to more efficiently control medical care delivery.
> 5. Group practices have become a feasible option for facilitating internal consultation and referral, remaining financially solvent, and meeting competitive demands in medical practice. This has been accompanied by a decline in solo and small group practices.
> 6. Health care organizations (particularly hospitals) are placing increasing emphasis on diversified services, in which the scope of medical care is broadened and linked to corporate strategy. Joint ventures by physicians with health care organizations have reinforced these trends in diversification.
> 7. There is a tendency for large-scale medical organizations to view physicians (and other staff members) as units of production. In large systems of care the contribution by any provider is less conspicuous. As governmental agencies and business corporations have discovered, large size may create numerous dysfunctions affecting the quality of working life and reciprocity between individual and organization.
> 8. Power is becoming concentrated in the hands of professional managers, who, despite their training and experience, may occasionally overlook the implications for clinical practice of organizational decisions. (7; from the *Journal of the American Medical Association*, Aug. 12, 1988, vol. 260, pp. 826–827. Copyright 1988, American Medical Association.)

American psychiatry now finds itself functioning in this highly entrepreneurial, highly competitive, and fiscally driven world in which the individual psychiatrist is called on almost daily to make decisions that often encroach upon and compromise his or her ethics as a physician.

> One of the more dramatic developments of the 20th century has been the transformation of the bilateral relationship between the physician as provider of care and the patient as purchaser and consumer of care into a multilateral relationship involving several parties. The physician is confronted with competing loyalties to and incentives from the patient; the health care purchaser, which may be a private corporation or the government; the insurer, which may be a private or a governmental organization; the health care institution (private or public) providing the

> services, which may be the physician's employer; and the government, which may attempt to regulate the free choices of these agents. (8)

Just as ethics cannot be separated from morality, Bill Webb has recently said that ethics and economics cannot be separated. I believe he is right.

Two codes of ethics for the medical-industrial complex, one serious and one tongue-in-cheek, will give you an idea of where medicine stands ethically. The serious one, written by Engelhardt and Rie, lists the following six rules:

> 1. *Tell the truth.* Health care providers should inform citizens, insurance subscribers, members of health maintenance organizations, and participants in other, similar health care endeavors about the limits on the services they seek.
> 2. *Help people buy what they want.* Not everyone values health care more than education, welfare, or other goods. Therefore, people should be allowed to purchase health care packages that provide limited or less than optimal care.
> 3. *Make a profit; economies involving scarcity are bad for everyone.* We live with a global economy in which increases in the availability of products and services—and the wealth they engender—are beneficial for everyone.
> 4. *Love thy neighbor, and be charitable.* The profit motive can lead to the solution of many but not all health care problems. Therefore, individuals, corporations, and governments should come to the aid of those in need.
> 5. *Honor, respect and advance the learned profession of medicine.* Learned professions have special obligations other than those of altruism and profit, such as commitments to excellence in knowledge and skill.
> 6. *Finally, market virtue. Combine the provision of health care services with a commitment to the rights and best interests of patients.* People are willing to pay for virtue and commitment. Besides, the profit motive without moral guidance is blind; moral inspiration without financial backing is bankrupt. (9)

The second code of ethics includes the 11 commandments according to medical economists:

> 1. To practice the most cost-effective medicine possible in accordance with the government guidelines.
> 2. To reduce admissions to hospitals as much as possible by maximizing outpatient treatment and facilities (realizing full well that this may prolong recovery of patients, jeopardize their health, and compromise my medical judgement).
> 3. To shorten hospital admissions by as many days as possible. To order no excessive diagnostics, employ only services absolutely indicated, and refrain from treating patients too vigorously. Quality of care cannot be allowed to compromise cost effectiveness!
> 4. To employ outpatient and same-day treatment services whenever possible, ignoring patient apprehensions and concerns about postoperative or post-treatment care and/or complications.
> 5. To cast asunder conscientious medical judgement and employ the most cost-effective medicine, procedures, and treatments as mandated by the government.
> 6. To conserve on medical diagnostics and treatments, thereby allowing health insurance companies to reap greater profits for the executives and shareholders. To aid, to the best of my ability, Medicare and Medicaid programs to reduce expenditures and conserve their funds so that these government agencies are not embarrassed by their inept management.
> 7. To admit to hospitals only those patients with current documented medical insurance policies or those with other documented substantial financial means, thereby avoiding financial stress on these institutions.
> 8. To accept, without question, government mandates, policies, and recommendations for outpatient and same-day procedures, diagnostics, and treatment regimens, hospital admissions, and for timely patient discharge.
> 9. To accept without question the medical judgements and decisions of our esteemed senators, congressmen, and other knowledgeable government executives, realizing full well that their decisions will adversely affect patient care.
> 10. To consider, above all, the "quality of life" and financial viability of all health insurance carriers and to cause no carrier undue financial strain.
> 11. To accept, without question, the ever-increasing financial and medicolegal burdens with malice towards none. (10)

The author concluded with the lament, "What hath government wrought?" (10). Both of these codes of ethics would make Hippocrates roll over in his grave.

That the ethics of the professions of medicine and psychiatry are inextricably bound up with profit and loss statements and with money as the bottom line is a profound statement. If this is true, and I believe it is, what can we in American psychiatry do about it? As psychiatrists we face a greater problem of double agentry than ever before. The question of whether the psychiatrist is the advocate of the patient or of the company—whether the psychiatrist's task is to take care of patients or control cost, whether he or she is constantly in a conflict of interest and wavering between clinical issues and fiscal issues—requires serious consideration and examination within our profession. The problems vary from gross and extraordinary efforts of blackmail and kickbacks, payoffs, and gross criminal actions to subtle but strong pressures that weigh heavily on the conscience of the average doctor.

The following quotation, which states the issue more eloquently, is from the report of the Hastings Center conference on new mental health economics and the import on the ethics of psychiatric practice.

> Limits on health care resources clearly are a fact of modern psychiatric practice. They are not a new phenomenon but have been given special emphasis by rising health costs and the response of the government and the corporate sector. Ethical consequences of limited resources include: abandoning patients without health coverage, particularly the aged, the poor, and the chronically mentally ill; diminished quality of care; a compromise of professional standards of care; and demoralization of the profession as manifested by an increased incidence of fraud and greed in psychiatric practice. (11)

By the year 2000 the vast majority of psychiatrists, if not all physicians, will be employed by corporations. The issue of double agentry will be even more intrusive. Dougherty's comment on the double agent commands our attention. He said, "One need not bow to for-profit corporations" (12). Forensic psychiatrists battle with this issue constantly, since the adversarial system and the psychiatrist as expert often force a clash of value systems. Misplaced empathy in such situations as disability benefits and stress in the workplace may not only injure the image of psychiatrists but lead some of our colleagues to lie in order that the patient benefit financially.

> One need not assume that all practitioners will yield to the new incentives nor that as a group they are especially venal. One need only observe that the structure of incentives will tend to incline professional relationships in a certain direction. If that direction is fraught with conflict between the interests of the provider and the patient, then, other things being equal, it is one to be avoided. Placing mental health professionals in a competitive economic environment does just that. It exacerbates the "double agent" problem by forcing professionals to serve both the interests of their patients and the interests of for-profit corporations. (12)

Very few, if any, of us went to medical school with the idea that we would be ripped apart by fiscal, legal, regulatory, and competitive forces. Yet it would be foolish to deny that they are there and play an important role in the day-to-day practice of our profession, that they distort clinical decision making, and that they are often very negative for patients. Sharfstein and Beigel in their seminal paper entitled "Less Is More?" (13), demonstrated that we live in an oxymoronic world in which the less care one gives, the more money he or she can make. What a way to live! Recently, reports of payments to increase the length of stay of patients in hospitals were revealed. Fifty dollars for each admission. Fifty dollars if you talk a patient out of leaving the hospital. Fifty dollars if you interfere with a patient's leaving against medical advice. Activities that were the natural and specific concerns of the doctor and the patient working together have now become the daily fare of the hospital administrator, the fiscal officer, and the director of marketing.

These unconscionable and illegal incentives have begun to drive the market so that we see a backlash in the press against inappropriate admissions to adolescent units, anorexia services, and psychiatric hospitals in general. Of course, the losers are those patients who do need hospitalization and have legitimate diagnoses that cry out for adequate and appropriate care. The losers are those citizens who use these horror stories to reinforce the stereotypes against psychiatrists and who may deprive many patients of appropriate and adequate care. We, the psychiatrists, are caught in the middle. We are then seen as the culprits, and the blame rarely goes to the hospitals; it is directly placed by the hospitals and the public at large on the heads of the psychiatrists who are "admitting these patients for their own pecuniary reasons."

Perhaps one of the greatest paradoxes of all in this era of cost containment is that as we destigmatize mental illness, more people will be admitted to hospitals and to outpatient services for care, and the view that psychiatric costs are uncontrollable will be based on that fact rather than on the truth that we have 40 million Americans who are in need of some psychiatric intervention. As it becomes more acceptable to seek help, the costs will rise appropriately rather than inappropriately, and for good clinical reasons rather than the touted fiscal reasons, that is, to line the pockets of hospitals and doctors.

The tarnished image that the public has of medicine and, by extension, psychiatry has been challenged by Smith, who stated:

> Few consider the possibility that a physician enters this chosen profession to make some contribution, however small, to his fellow man. Medicine is a calling. Physicians possess knowledge and skill derived from years of education that set them apart from, but not above, the general population. Although the source of the physician's income is accrued largely from medical practice, motivation to perform these services goes beyond financial. (14)

The ethical milieu in which we find ourselves escalates the dichotomy between Smith's virtuous doctor and the kind of behavior that I have described earlier. The doctor will carry these burdens because quality assurance and quality care are in the hands of physicians. As a profession, we are weakened by those among us who are the weakest. Our ability to act in concert regarding issues of professional ethics and standards of care that are of the highest quality is compromised by those doctors who, because of their own inability, cannot fight the hospital administrators, cannot stand up to the hospital's demands, and do, in fact, compromise the profession by compromising their own ethics. I write from the unfortunate position of a physician imbued with an old-fashioned ethical standard in which the doctor's struggle between selfishness and selflessness is never resolved. Rather, it is a constant ethical dilemma that tears at the doctor, who must waver between his or her family and patients, private life and patients, and lifestyle and patients. In a recent article Volberding stated:

> the complexities of AIDS care force us to reconsider our health care systems, to ask ourselves whether our system is functioning well, and to be prepared to revise that system when needed to enable us to deal with the medical, psychosocial, and ethical problems of AIDS. Many physicians avoid assuming an AIDS care role because of its accompanying burdens and stresses; while some of these can be addressed through intensified professional education, others may require new regulations or standards of conduct within our profession. How well the health care professions will develop and monitor these standards remains an important but unanswered question. Let us hope that we will find qualities in ourselves and in those around us that

> will improve our efforts, and let us not forget the humanity that we all share. (15)

It is difficult for me to understand one phrase in the preceding paragraph: "Many physicians avoid assuming an AIDS care role because of its accompanying burdens and stresses . . . ." The subtlety of the distortion of old-fashioned ethics could easily be lost on a new, young physician who sees this as unilaterally consistent with the world view that he or she has brought to the practice of medicine.

In contrast, Pellegrino wrote on the issue of ethics in the care of AIDS patients, "necessary as virtue is to medical ethics, it is not sufficient and we cannot rely on the return of the virtuous physician who will instinctively grasp the duty of altruism" (16). He listed three things specific to medicine itself that

> impose an obligation of effacement of self-interest on the physician and distinguish medicine from business and most other careers or forms of livelihood. These are:
>
> 1. The nature of illness itself. The sick person is in a uniquely dependent, anxious, vulnerable, and exploitable state. Moreover, physicians invite that trust when offering to put knowledge at the service of the sick. A medical need in itself constitutes a moral claim on those equipped to help.
>
> 2. The knowledge the physician offers is not proprietary. It is acquired through the privilege of a medical education; and
>
> 3. This covenant is publicly acknowledged when the physician takes an oath at graduation. This—not the degree—is the graduate's formal entry into the profession. (16)

STANDARDS FOR PSYCHIATRY

During the last few months, we have moved toward the development of a set of guidelines for the behavior of both doctors and hospitals. Fortunately, we have been joined by the National Association of Private Psychiatric Hospitals, the Federation of Hospital Chains, and the Academy of Child and Adolescent Psychiatry, all of whom have grave concerns that unless we are able to clean up our house and essentially be purer than Caesar's wife, we will be the victims of an escalating negativity that ultimately will cause further deterioration in the care system for millions of Americans with mental illnesses and emotional disturbances.

These guidelines must clearly spell out where the fiscal role takes precedence and where the doctor-patient relationship is primary. They also must address the ethical limitations of entrepreneurial activity. Can individual psychiatrists make a living, given these conditions? Will the guidelines be so anachronistic that they will try to recreate the 1950s in the 1990s? Are we going to make it easier for litigious patients and their lawyers to sue us and destroy us? I think not. I think, rather, that we can be heroic. We can take the high road. We can stand for what physicians have stood for for thousands of years since Hippocrates. We can adhere to the oath that Dr. Pardes will administer to all of the new Fellows, reinforcing their commitment to our patients and to our role as healers, ministers, and providers of extraordinary, scientific, biopsychosocial care. In order to do this, in addition to the guidelines for ethical behavior in the economic world that I am suggesting, we need to develop standards in three specific and important areas and we need to embrace a comprehensive, scientifically driven biopsychosocial definition of our profession and paradigm of our practice and training.

The three areas for standard setting are diagnosis, treatment, and training. In the area of diagnosis, we have, through the development of *DSM-III-R* and the imminent *DSM-IV*, developed a model that has become international and has had the results that many earlier pioneers thought Esperanto might have—breaking down barriers and pushing a level of uniformity through criteria setting never before achieved in the history of psychiatry. This book has been translated into approximately 25 foreign languages. The goal, to develop a universal, scientific, proven diagnostic scheme, is well on its way. It is not a perfect volume, and we look forward to improvements that will incorporate new scientific evidence in the areas of demography, nomenclature, and diagnostic and descriptive psychiatry.

We need to make a similar effort with regard to treatment. I agree with those who feel that a manual for treatment is inappropriate and would be a cookbook kind of meaningless endeavor that would suspend clinical judgment and reduce the value and importance of the physician. Clearly, from what I have already written, the physician's role is paramount and the need for innovation and creativity in the therapeutic process remains very important. Nevertheless, we have clearly entered an era of important scientific development, and our treatment approaches cannot be so creative or innovative that they are idiosyncratic and, in the final analysis, detrimental to patients. We must, through a series of well-designed efficacy studies, bring the rational treatment of patients, uniformly treated throughout the United States and the world, into the forefront of psychiatry. This is a tall order. At the 1989 Annual Meeting the book on treatment methods in psychiatry, edited by Dr. Byram Karasu (17), was put on sale for the first time. It is a small beginning toward the goal of treatments that are specific to the illness, are well documented, and are shown to be effective, and it represents an approach to the field that will make the treatments in psychiatry not only well understood by the psychiatrist but accepted by the patients and the public.

The third area in which standardization is seriously needed is training. It is imperative that every graduate of every psychiatric training program in the United States be a high-quality psychiatrist. Everyone knows that that is not currently true. There are both inferior programs and inferior trainees. A combination of an inferior program and an inferior trainee is devastating to the future practice of psychiatry, since that person will be in practice for 30 or 40 years and will be a detriment to the field. This seriously damages any efforts we make to increase our credibility by means of improving our ethics.

Most important is the acceptance throughout our country and throughout all psychiatric training programs of a position clearly enunciated by the Residency Review Committee—that the training must be biopsychosocial and that the treatments carried out as a result of the training must be biopsychosocial. This position must be well incorporated into every training program in the country. There are, in fact, multiple ways to approach the treatment of certain illnesses. I have watched with amazement Dr. Habib Davanloo cure a patient with panic disorder after a limited number of treatment sessions with his unique methodology and without any medication. I have also seen the use of antianxiety and antidepressant drugs create an extraordinary change in the ability of panic disorder patients to return to a functional life. The combination of drugs and specific psychotherapeutic regimens has had an important effect on the changing panorama of treatment modalities for specific illnesses.

Each trainee must have an acquaintance with *and* the capacity to carry out multiple forms of therapy for specific illnesses. If trainees only learn one form and it is a good one, that is fine. But to learn a methodology that is narrow and an approach to psychiatry that is neither broad nor uniformly applicable will, in the long run, hurt the profession and demean the level of scientific endeavor. It is truly in the area of science where the future of psychiatry is most bright and where optimism can be continually maintained over the next decade. Our science—not only neuroscience but also behavioral science—is strong. Those of us with gray hairs must avoid trivializing one kind of psychiatry to exalt another and must try to be broad based; and we must be willing to train young men and women so that they can be biopsychosocial and practice a form of psychiatry that is modern and broad.

CONCLUSIONS

Every time I write or think about ethics, every time I hear a discussion about ethics, I am forced to reexamine my own ethics and values. I try to decide if I have come down on the right side of the issue. There are so many places in our professional lives where there is the opportunity to wander, knowingly or unknowingly, into unethical areas that we must be vigilant and recognize that the effect of each unethical act damages us all.

We must also have the courage to draw the line, even if it causes anxiety, even if it costs us money. A decade ago, the then president of the Pennsylvania district branch signed a letter that essentially advised the members that it was unethical to sign either prescription blanks or commitment papers which a nonphysician would subsequently fill in. To our amazement, 20 colleagues wrote to the district president expressing gratitude for the letter and saying that they had taken it to their administrators and said, "We can't do this anymore; our association says it's unethical."

The APA should and will encounter the limits of compromise. I believe it is the proper role for a specialty society. Another conclusion of the Hastings Center report reads as follows:

> The clear enunciation and enforcement of our ethical standards of practice is [*sic*] critical as we make the transition into the new health economic environment. The modern psychiatrist practices in a very uncertain economic atmosphere under increasing pressures that could compromise his covenant with his patient. Potential conflict of interest situations such as physician ownership of equipment or facilities should be examined carefully to avoid compromising patient care. Practice arrangements that would result in fee-splitting (providing financial incentives solely for the referral of patients) should be avoided. Cases of suspected fraudulent billing should be reported and evaluated for ethical misconduct. (11)

Smith has described our choice forcefully and elegantly:

> Medical science has made vast strides during the past 50 years. Now, we must keep pace on the socioeconomic side as well. We need to decide whether we will be co-partners (with government, hospitals, insurers, etc.) in the future development of medicine or whether we will become employees. In the former role, we will be able to help direct medical progress; in the latter, we will sacrifice the ethical commitment we have for our patients. (14)

I believe that the specialty of psychiatry can lead the rest of medicine to a higher ethical plane. We should not do violence to our patients by fiscal manipulation any more than we should have done violence to our patients years ago through inappropriate incarceration and the use of treatment methods that were harmful rather than helpful. In our rapidly changing world, the patient must still be able to rely on his or her psychiatrist and to depend on the psychiatrist's skill, judgment, knowledge, and ethics. We demand that our young people practice a modern and unusually new kind of scientific psychiatry and at the same time adopt a humane and somewhat traditional view of our profession and its ethics, standards, and compassion. We must ask young psychiatrists to recreate ethical standards for medicine and psychiatry in which treatments and compassion are integrated and uncompromised. This is a difficult, if not impossible, task to ask 35,000 people to join in. However, the future of our world and our profession demands it. The covenant between patient and doctor will foster it, and the continuing, successful effort to destigmatize not only the mentally ill but their care givers will provide fertile soil in which future generations of psychiatrists will practice, hopefully without the struggle created by so many issues and problems.

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Response to the Presidential Address: The Research Alliance: Road to Clinical Excellence

Herbert Pardes, M.D.

Psychiatry is at a crossroads. New information is exploding around us. Urgent clinical needs are colliding with severe economic boundaries. The stigma of mental illness is lifting a little; people are bravely unmasking themselves. But domestic policy in this country is predominantly driven by the deficit. As a result, resources to address the problems of mental illness, drug abuse, and acquired immune deficiency syndrome (AIDS), which have reached crisis proportions, are inadequate.

In addition, this country's value systems are in upheaval. We are not at war, but these days many Americans seem to regard one another as enemies. There has been an unleashing of excessive zeal in several guises. Television cameras portray thousands blocking entry to an abortion clinic, because abortion is "always" wrong. Animal activists state that a "bloody vivisector" will die this year and declare their readiness to disregard laws and penetrate steel and concrete to stop research on animals.

In the midst of this conflict, psychiatry must define its own credo. It must chart its course through a complex landscape. Where do we stand? What concerns us? What will we fight for? How are we doing, and how can we do better?

To turn again to the larger context: There will be in any open society a multitude of ideologies; that is healthy and welcome. But when any of these influence national policy—in particular domestic spending—to the detriment of a great many people, it is time to give them a hard look.

One conspicuous contemporary value system—if that is the right term—is a preoccupation with money, property, and the power to get more of the same. Here, other people's lives are of no concern. At the same time, an upsurge of intolerance now forms the basis of several "movements." All of them demand that laws be changed to suit them. One group interferes with a woman's choice of whether to bear a child. Another argues that medical researchers are abusing the "rights" of animals. Proponents of these views are more than willing to prevent other people from exercising *their* rights. Some rights, apparently, are more right than others.

Another would-be value system is to absolve people of all responsibility and to blame everything on forces beyond our control. Johnny does not hold a job because he is disillusioned with society. Mary is not accountable for using drugs, because her friends do. Billy is not learning because his teachers are no good. There is nothing wrong with me; change the outside.

The fact that people are free to hold different opinions is vital to this country's richness—not the kind that buys Porsches and condominiums but what is generated by cultural, intellectual, and creative energies. Nevertheless, I believe that we have some fundamental values as a nation and that we must uphold them. I also believe that some of psychiatry's values are harmonious with these.

Along with diversity, American values include fair play, with a system of justice that tries to ensure it; free speech and tolerance; honesty and courage in the face of criticism or danger; caring for our neighbors; hard work, which should be rewarded; and pride when national actions are informed by these values and, conversely, a feeling, when the nation departs from them, that its leaders and their constituents, not the country itself, are wrong.

It is common now to see signs that these high ideals are in trouble. The signs include obliviousness of people lying in the streets; government condemnation of dealing with a country that holds our citizens hostage, while our same government secretly sells that country weapons; book companies that withdraw a work of fiction for fear of the religious reaction; a budget structure that protects the corporate pocketbook, while 37 million people are without health insurance; and rationed health care to the elderly, and health care provider institutions foundering for lack of resources, because the government will not ask the taxpayer to contribute and will not decrease its military spending.

These signs are in troubling contrast to the original spirit of the country, in which the country thrived in ideological terms as well as in goods and services. Contemporary examples of crassness, hypocrisy, and lack

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of fellow-feeling are especially offensive to us and to members of other medical and service professions.

To turn now from our country's situation, what about our profession's? We in psychiatry must maintain *our* high standards; we, too, must be self-critical. We must not be divided and weakened by self-interest or largely specious internal conflicts. Ours is an intellectually far-reaching discipline, with bridges to the social sciences and the humanities as well as the rest of medicine. Psychiatry is also mission-oriented, and it is important to assess our progress in that mission. What we have in common is of such importance that for any group of us to take a superior stance toward another group is inappropriate.

VALUES AND ACCOMPLISHMENTS OF PSYCHIATRY

Many of the values shared by psychiatrists are lofty. They include a desire to help people in mental anguish, who have long been ill-understood and stigmatized; a fascination with human behavior, with the uniqueness of individuals, and with the endlessly varied biopsychosocial spheres in which they evolve; a powerful belief that one should be slow to judge but generous with compassion; a corresponding distaste for the simplistic, the exclusively technological, and the mindlessly repetitive; and a longing to see the causes of psychiatric illness clarified and treatments and preventive measures made better.

With respect to these ideals, how are we doing? We are doing well, although much remains to be done. We can take satisfaction in what we have accomplished. I count myself an optimist and a chauvinist for psychiatry. Here are some of the reasons.

1. Psychiatry has fostered attention to nuances of communication and behavior and to the previously unrecognized forces that influence them. It has worked to decipher seemingly unintelligible behavior and to encourage compassion toward people with mental illness.

2. Psychiatry has placed itself squarely within the field of medicine. This is a major accomplishment. The deletion of the internship requirement in the early 1970s was unwise, but the swift reaction and the reinstatement of the internship showed that psychiatry identifies itself as a medical specialty.

3. Treatment, diagnosis, and epidemiology have steadily advanced. Clinical concepts and interventions have been refined and made much more specific. There is a growing consensus worldwide about psychiatric diagnostic criteria. This consensus facilitates research, treatment, and communication. We have increasingly informative epidemiologic data, based on solid methodology. We have learned from these findings that some 15% within 1 month, or 19% in 6 months, of the people in this country suffer from a diagnosable psychiatric illness (1). We have also learned that certain disorders, for instance, obsessive-compulsive disorder, are far more frequent than we knew (the rate may be as high as 3.3%) (2).

There have been major advances in our treatment methods over the past two to three decades (3). Lithium alone has saved some $6 billion in mental health services in the last 15 years. We can now also offer tricyclics, monoamine oxidase inhibitors, carbamazepine for patients unresponsive to lithium, neuroleptics, clozapine for patients unresponsive to standard neuroleptics, clomipramine for obsessive-compulsive disorders, antidepressants such as fluoxetine—with action specific to one transmitter system, thereby decreasing side effects—and a range of combined pharmacological and psychosocial interventions for panic disorder. ECT has been refined to reduce side effects, and patients to whom it is offered are now more carefully selected, with improved results.

There have also been developments in time-limited, dynamically oriented psychotherapy, crisis intervention, multiple-family group treatment for families with schizophrenic relatives, and new methods in behavioral treatments. New methods are also being developed for the evaluation of the psychotherapies. There is new evidence that specific kinds of psychotherapy are effective in the treatment of some depressions (4).

Thanks to this work, psychiatrists can make much more informed judgments about what treatment to use and when to refer a patient to a colleague. The days when a patient's treatment depended on the psychiatrist, rather than the diagnosis, are ending. Patients can now receive the benefit of an expanded and more specific therapeutic arsenal, and as a group we are much more effective physicians.

4. The past two decades also represent an extraordinary era of progress in our research. The revelation that the brain has 10^{12} neurons, making an average of 1,000 connections with at least 50 transmitters and, as a rule, with several different receptors for each transmitter (5), confirms that human behavior reflects an awe-inspiring biological infrastructure. Some 25% to 35% of the 50,000 to 100,000 genes in the human genome affect the brain. Molecular geneticists have located genes for two kinds of manic depression, for Alzheimer's disease, and possibly for one type of schizophrenia (6). Preliminary data suggest that there may be a gene on chromosome 16 for a substantial subgroup of panic disorders (7). Imaging technology has shown temporal lobe changes (8) and ventriculomegaly in schizophrenia (9). It has also shown changes in cerebral blood flow in some panic disorder patients (10). Changes in regional cerebral blood flow now appear to be detectable in the early stages of Alzheimer's disease (11). If this finding is substantiated, it would provide us with an early diagnostic tool for Alzheimer's. Imaging has also suggested changes in brain function in patients with obsessive-compulsive disease (12).

Meanwhile, galvanized by energy throughout the field, the biological and psychological sciences have been moving toward each other (13). Many studies have shown that emotional states are related to neurotransmitter activity. There is growing evidence that emotional states may modify processes of the immune system (14). A neuroanatomical hypothesis was recently put forward for panic disorder, attempting to integrate both biological and psychological aspects of the illness (15). We are gradually discovering the biological mechanisms by which learning and memory take place, and we are also recognizing the malleability and plasticity of brain tissue (3). If we can actually identify specific brain defects in specific psychiatric illnesses, they may someday be reparable. This work is tantamount to a golden age for psychiatry as a medical science.

5. This flood of new information has not gone unnoticed by the rest of the scientific community. In the last 9 years, two Nobel Prizes, five Lasker Awards, two American Mental Health Fund Awards, two Lieber Awards, one National Academy of Sciences Award, and two Presidential Medals have been given either for research on psychiatric illness and treatment or for research with application in psychiatry. This remarkable record documents a recent statement by Lewis Thomas, the dean of biology-watching, that neurobiology is currently the most exciting of the biomedical sciences (16). Thomas also noted that our notions of mind and brain and how they interact are likely to be revolutionized in the next few decades.

6. There have also been remarkable contributions by other psychiatrists, outside the field as well as within. Our discipline has produced a National Medal of Science winner, a congressman, a president of one of our major foundations, a president of one of our major universities, deans of medical schools, university vice presidents, a Pulitzer Prize winner, and international heroes, exemplified by Dr. Anatoly Koryagin, who are not afraid to challenge a system with immoral policies.

When I speak to young people about possible careers in psychiatry, I am pleased to be able to tell them what a rich menu of opportunities is before them. Our interests range from psychiatry and the law to psychiatry and the neuron to psychiatry and psychotherapy.

And more young people are joining us. Medical students, one of the most critical audiences, have been quick to appreciate the new excitement and stature of psychiatry. We were at our peak in attracting students at the end of the 1960s, when some 10% of senior medical students chose psychiatry. In the 1970s, a very difficult decade for us, that number dropped to about 3%. In the 1980s, interest has risen again, and we are now up to 5.5% (17).

I am happy to add anecdotally that some of the best medical students in the country are choosing psychiatry. It is exhilarating to look at the new applicants and see the breadth and variety of their backgrounds. Another sign that the word has spread about psychiatry is that more support is being made available to fledgling psychiatrists. More fellowships are being offered by both public and private sources for careers in psychiatric research, geriatric psychiatry, substance abuse, child psychiatry, and many other areas. I am also happy to note that over 90% of current residents are members of APA.

The notion that psychiatrists went into their field in order to conquer their own problems will take its proper place as a notion of historic interest. It goes without saying that we are interested in our own behavior and attitudes, along with other people's. But introspective powers are a strength, not a liability. Better the men and women who know themselves and their human imperfections, rather than people who are oblivious of them but may still be driven by them.

7. If our newcomers are a credit to us, our leadership is increasingly effective. An alliance of dedicated individuals has been restoring the capabilities and resources of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). From 1969 to 1976, a period that was distressing in terms of policy makers' decisions about research support for the field, the budget of the National Institute of Mental Health (NIMH) actually went down $5 million. That was also a time when NIMH was out of touch with the concerns of many psychiatrists nationwide.

But since 1977, the NIMH research budget has increased to $294 million: to $345 million when one includes research training, demonstrations, and administration. I felt honored to have the opportunity to help initiate a period of growth in research at NIMH. I felt we began to make it more representative of the field as a whole. We moved it toward psychiatric disorders and related neurobiological and behavioral sciences. In those years, we created the first neuroscience branch at NIMH, activated the schizophrenia center, started a center on disorders of children and adolescents, moved toward creating a program in prevention research, and closed programs of only vague relevance to mental illness. The vigorous spirit of those days continues with our new leadership at ADAMHA and NIMH. Last year a coalition of professional and citizen groups banded together and secured the largest boost in all of NIMH's history: over $40 million. We must see that the budget continues to rise.

The leadership of the APA medical director's staff has also been outstanding. In the fast-paced world of Washington, informed, sophisticated, and courageous leadership is vital, and we have been fortunate to have it.

8. One of the most important recent accomplishments is the first major improvement in reimbursement for psychiatric care under Medicare after 25 years of effort. This is a monumental victory on behalf of all the mentally ill. Having worked for years in the late 1970s and early 1980s to try to secure some change in this area, I can say from experience that it was a formidable task.

In addition, Jay Cutler, APA Director of Government Relations, recently succeeded in getting a substantial mental health package included in the Kennedy Minimum Health Benefits Bill now before the Congress. In New York, the area Council succeeded in getting Governor Cuomo to direct that some of the discrimination against psychiatric disorders in insurance policies be eliminated.

9. One of the most vital developments of the 1980s is the rise of citizen groups. The National Mental Health Association has regained vigor and is reasserting itself as a force for research as well as for clinical programs. The National Alliance for the Mentally Ill, which was started in the early 1980s, now has branches in every state in the country, with over 75,000 families as members. The National Depressive and Manic Depressive Association, which until 1986 operated primarily in the Chicago area, has become a national organization and a vigorous partner in the citizen/professional collaboration. The American Mental Health Fund continues to make a strong public education effort. With support from the National Advertising Council, it has been fostering the awareness that psychiatric illness is like any other medical condition and must be taken seriously. There are other citizen groups, including the Phobia Society of America, the Obsessive-Compulsive Disorders Foundation, and the National Mental Health Consumers' Association.

A particularly outstanding example of the citizen enterprise is the National Alliance for Research on Schizophrenia and Depression (NARSAD). This fast-growing group started with the modest goal of giving $50,000 in grants in 1987. Its scientific council includes psychiatrists and other scientists from all over the country. And it is collaborating with most of the other major citizen groups, including several mentioned earlier.

The $50,000 that NARSAD began with grew almost overnight to a quarter of a million dollars. In 1988 the group awarded over $1 million. In 1989 it has already awarded $1,890,000. NARSAD has a goal of $100 million by the year 2000. It sponsors the largest prize given on a regular basis only for psychiatric research, the $50,000 Lieber Award. With these new grants, NARSAD will have funded 78 psychiatric investigators in its short life.

I am happy to say that APA helped to launch NARSAD, as did other groups including the Charter Medical Corporation. As a result, we now have an organization analogous to the American Cancer Society, the American Heart Association, and the Multiple Sclerosis Society to supply private research support that supplements the government's contribution. It is high time. The Presidential Commission on Mental Health indicated that over 85% of all money for research on psychiatric illness comes from the public sector (18). This figure is in sharp contrast to the approximately 58% for other medical disciplines.

While there has been some tension between the citizen groups and professional groups, it is usually transient. Overall, there is a readiness to pull together and move beyond minor differences to the major goal of making a concerted attack on mental illness and discrimination against mental illness.

I count myself deeply fortunate to be a psychiatrist who may witness the decline of the stigma against the mentally ill in my own lifetime. It was Paul Fink's express mission during his tenure as our President. It is a guiding mission for all of us. The progress we are seeing represents a reward for all our efforts: the giant steps of our science and our treatments, the long fight of our patients and their families, and the citizens' new posture of comradeship toward the providers, who have devoted their professional lives to helping them.

CHALLENGES FACING CONTEMPORARY PSYCHIATRISTS

That we can take pleasure in some accomplishments does not diminish the challenges. Some are old and familiar, and some have arisen as the landscape has changed, both within the profession and around it.

1. Health budgets at national, state, and local levels continue to tighten, in part due to the demand for beds created by increasing numbers of AIDS patients.

2. Outside authorities intrude more and more and continue to impose more regulations.

3. Interdisciplinary tension within the mental health field is high, with multiple arguments stemming from reimbursement issues.

4. Some of our members worry that if we do not subspecialize, appropriate psychiatric involvement will not occur in areas such as substance abuse and geriatrics. Simultaneously, some see a danger to general psychiatry if too many of us subspecialize.

5. Tension has sprung up among psychiatrists because of information generated by research. In particular, clinicians educated during the age when psychodynamics dominated training now feel threatened by the array of new biological approaches.

This tension is a problem that we must address. It is the duty of APA, along with other academic organizations, to provide opportunities for our clinicians to become up-to-date, primarily to provide them with knowledge regarding the best possible therapeutic resources for helping their patients, but also so that they can participate in the excitement of our scientific progress. We should prepare for a particular effort with developments in areas such as genetics, where discoveries may have profound psychological and psychiatric implications. We should encourage clinicians to add new skills, made possible by research, to supplement and complement knowledge and ability in psychodynamics.

Modifications in the APA annual meeting program have begun to address this need; more efforts will be forthcoming. While movement toward some form of recertification is not a cure-all, it will spur all of us to keep abreast of new developments. It is also vital that academic institutions deliver first-rate and current education to psychiatrists in training. Only by moving simultaneously on several fronts can we expect to educate all of our 35,000 members, who represent most of the 37,000–42,000 psychiatrists in the United States.

Another reason for psychiatrists to be scientifically well-informed is that patients and their families are going to demand it. In itself, the desire for more communication is a healthy development. It reflects the growing partnership between our profession and the public. But there is no question that it puts new pressure on us. A major tenet of our training was that clinicians should be most cautious about discussions with family members. However, this point is a particularly distressing one to many families. The times have changed, and we must be willing to find ways to reconcile these different perspectives.

In the foreseeable future, patients will decide where to seek out psychiatric treatment by finding out where they can get the best care available for their specific trouble. This is as it should be. To help them, we must all be informed of the latest refinements in diagnosis and treatment, and be prepared either to offer a broad spectrum of therapies, or to refer patients appropriately.

6. Another challenge has arisen in the form of distasteful behavior within our own ranks. Some scientists have ridiculed clinicians, when what they should be doing is helping educate their clinician colleagues. Clinicians behave just as inappropriately when they ignore new research findings or even try to sabotage research. This is no time for psychiatrists to play omniscient, least of all with one another. Complacency, parochialism, and intellectual indolence are not acceptable in modern psychiatry.

There are occasional instances of unethical conduct by psychiatrists, resulting in patients being victimized. All such episodes must stop. APA has been vigorous and effective in dealing with these offenses, and it will continue to be. Not only must the public have confidence in us, but we must have fully justified confidence in our own profession and our colleagues.

THE ROAD AHEAD

But the remarkable prospects for psychiatry far outdistance our problems. We will rise more and more in the public esteem as we continue to deliver more and more effective treatment. Our new research is being increasingly appreciated throughout the medical science community. Greater numbers of young people are entering clinical psychiatry and psychiatric research. They will find their chosen field at least as fulfilling as it was 20, 30, or 40 years ago. We have a new and increasingly powerful citizen constituency. And we are determined as a group to ensure that the attack on mental illness is given due support by policy makers.

Paul Fink's theme was the fight against stigma. I am calling mine "The Research Alliance: Road to Clinical Excellence." But our ultimate goal is the same: the relief of psychiatric distress. Scientists, patients, families, citizens, educators, and government leaders are now allied in working toward better care for the mentally ill, and it will be as allies that we will move forward with full vigor. We are building the road to make our progress as fast as possible. The materials we need will come from several sources, some of which I wish to emphasize.

1. We must see to it that the NIMH budget for the attack on mental illness continues to grow. We hear congressional concern for work on other problems, such as AIDS and drug abuse. We agree that other areas need attention as well, but not at the expense of increased funding to fight psychiatric illness. The $345 million NIMH research budget should be raised to $500 million and raised this year.

2. We must all—professionals and citizens alike—make it known to policy makers that animal research is a central part of science. There will be no cures, no vaccines, no new treatments without animal research. The notion that alternative systems can be used is wildly overstated. We certainly want animals to be treated well, and we want them to be used as sparingly as possible. But the three chief strategies by which animal "rights" groups intimidate scientists, and sometimes succeed in eliminating research, must be exposed and defeated. These strategies are the isolation of one individual scientist for intimidation, lobbying for legislation that would block animal research, and the development of multiple regulations to make animal research so expensive that research institutes and academic centers cannot afford it.

I urge all psychiatrists: If you care about progress in psychiatric medicine, about doing our absolute best for our patients present and future, we must make our position clear. We must advocate animal research. We must educate policy makers. We must, in numbers, alongside the citizen advocates who are trying to help us, write to Congress and to the Executive branch. We must forcefully show that the overwhelming majority of Americans, while wanting animals to be well cared for, also want to see diseases conquered. To treat and cure most disease, in animals as well as in human beings, there is no alternative to research with animals and human beings.

3. We must support private efforts to develop resources for research in mental illness. If we all made a modest contribution to NARSAD, we would know that the money was going to support research on the major mental illnesses, all over the country and all over the world. I urge you, and everyone alarmed by the toll that mental illness takes on human beings, to contribute to this organization. NARSAD is dedicated to fostering research that will provide clinicians with more and better skills, which will enable them to offer more and better help to the patients who so sorely need it.

4. We must extend ourselves to more citizen groups. What we are doing with the citizens is working. We should do it even more. We have to sustain and encourage these people in the monumental effort they are making.

5. The distance between our basic science and our clinical applications will decrease in the years ahead. Correspondingly, there will be more interdisciplinary activity, including education and collaboration among ourselves. The more this happens, the better. I urge you to engage with one another in collegial pursuits.

These will enrich all of us and add to the resources that each of us can draw upon in helping patients.

6. We must place responsible and effective representatives before the public, to speak on our behalf about our concerns. I intend to do this as aggressively as possible, and I will call on all the strength of American psychiatry to help.

Thinking both of our role in the delivery of clinical psychiatric services and of the way we are perceived by the public, I want to make a final point about where I think psychiatry should be going.

We are all aware of the devastation that mental illness causes. I would like to call your attention to the excellent lead article by Erica Goode in the April 24 issue of *U.S. News and World Report*, entitled "When Mental Illness Hits Home" (19). The article traces the life of a young woman, who went from being a delightful, talented child to being a victim of schizophrenia. The result was a living hell for both her and her family, until at last the woman died. To quote the article:

> Everyone likes Janet. Graceful, smoothly drawn figures appear under the expert control of her pen. Of the sisters, she is the superior athlete, a proficient skier, dexterous with a hockey stick. She laughs easily, glides effortlessly through her seventh-grade classes.

Her sister remembers, "She was so pretty. I wanted to look like her, to be like her." We then hear what life was like for Janet's mother some years later:

> After months of silence the telephone would ring in the darkness, startling Mary Alexander from sleep. "Do you have a daughter?" The voice blandly official, the caller in some other town or state, in Minneapolis this time or Pittsburgh. "Mrs. Alexander, do you have a daughter?"

She would close her eyes waiting for the next words, bracing herself for them.

> "Mrs. Alexander, do you have a daughter who is living on the golf course and disturbing neighbors?" "Who is walking down the street in mid-December with no clothes on . . . . Who tried to throw herself in front of a bus . . . . Mrs. Alexander, we have your daughter here in the hospital . . . ." In her mind are images of Janet years ago: building a fort with her three younger sisters, her blond hair in long straight locks; Janet on the chair lift with her father in Aspen; reading, curled in the window seat of the big New England farm house.

The stricken mother finally says, "I swear to God, I would rather my child had cancer than this agony of a disease."

The article describes many of the miseries of schizophrenia and other mental illnesses, including society's tendency to look in the other direction. But a note that especially disturbed me, and which I believe will disturb you, was the suggestion that we are part of the problem. The article refers to "the values of a psychiatric profession that rewards private practice and economically penalizes those who choose to work with the severely ill in the public sector."

There is, of course, no question that it is not psychiatry alone that follows economic incentives or controls the forces that determine how medical treatment of any kind is subsidized in our society. The talented journalist acknowledges that other pressures are at work. My concern is not to dissect this particular article. My concern, like yours, is to help the unfortunate people who have no one to turn to but us. Above all else, we must bear in mind that we are doctors taking care of people in trouble. We must continue to be guided by the beliefs that led us to enter psychiatry and to dedicate ourselves to it. Centuries ago, Seneca captured the plight of people wrestling alone with life's pain in words that could come just as well from our patients:

> Listen to me for a day—an hour—A moment!
> Lest I expire in my terrible wilderness, my lonely silence.
> O God, is there no one to listen?

In psychiatry, it is a point of pride that we listen to people who hurt, that we listen with all three ears. Like all physicians, we treat people for whom the pursuit of happiness might otherwise be impossible. But we must be honest with ourselves. Are we earning the right to that pride, the pride we take in being physicians? Are we devoting ourselves to helping troubled people, who are supposed to be our foremost concern? Each of us must ask these questions. And we must be able to answer, Yes.

We live in times that are venal and self-righteous, when softhearted lip service may be just another way of opting out. These are times when people step over half-conscious bodies lying on the sidewalk. These are times when scientists, who have accepted the sad necessity of sacrificing experimental animals to save human lives, are harassed, insulted, and threatened, and our information base is in very real danger of being jeopardized.

These are not times in which we as psychiatrists can allow ourselves to be preoccupied with petty rivalries and partisan concerns. We are not competitive businesses waiting to attack one another's turf. Any fighting we do must be in the best interests of our patients and of our ability to help them. We will assert and defend our concerns as a healing profession. We must also conduct ourselves with the dignity of a healing profession. However widely the popular culture may measure its value in terms of yachts, we must continue to measure our own as lifeboats for struggling people.

Our field has always been in some ways controversial. Inasmuch as psychiatry holds up the mirror to the complex nature of human life, perhaps it always will be. But it just might be that psychiatrists, as students of human behavior, may help to influence this country's attitudes for the better. We are certainly trying to do so: Our hope is that before and after "pictures" of the stigma against mental illness, taken some years ago and perhaps a few years in the future, will reflect those efforts.

Yes, in some ways we have made progress. But we still have our work cut out for us. If we recognize—along with friends and colleagues involved in the mental health enterprise, both in and out of psychiatry—that we have much ground in common, and respect and appreciate one another's contributions in all their diversity, we will find one another to be powerful allies in the worthy cause that we all share. I am proud to be a psychiatrist. I hope you feel the same.

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Paul J. Fink, M.D., One Hundred Seventeenth President, 1988–1989

Carolyn B. Robinowitz, M.D.

When Paul J. Fink became a bar mitzvah, the rabbi predicted to the congregation that when he grew up, he would become president of a synagogue. By the age of 13, his qualities of scholarship, caring and involvement, and energetic leadership were apparent. In his career as a psychiatrist, Paul Fink has demonstrated the same skills that so impressed his rabbi decades ago, and these same qualities have marked his tenure as the 117th president of the American Psychiatric Association. Energetic, involved, and committed, with a zest and passion for the practice of psychiatry and the care and relief it can bring patients, he has used the presidency as a platform from which to espouse his involvement and concerns and, in particular, to once and for all abolish the stigma that so plagues the profession as well as our patients.

Paul Fink is the older of two sons of John and Essie Fink. His late father was an electrician, as well as a leader of marathon bands, and from him, Paul may have developed the special love of music, particularly opera, that marks his life. His brother Ted followed his father's other career and became a builder.

Paul Fink is truly a son of Philadelphia. Born there in 1933, he completed elementary and high school in the Philadelphia public school system. A magna cum laude graduate of Temple University with honors in biology, he also received his M.D. degree from Temple in 1958. He completed internship and residency in psychiatry at the Albert Einstein Medical Center and Philadelphia Psychiatric Center and completed his training in psychoanalysis at the Institute of the Philadelphia Association for Psychoanalysis in 1966. He currently is Chairman of the Department of Psychiatry at Albert Einstein Medical Center and Medical Director of the Philadelphia Psychiatric Center.

After his residency, he joined the faculty at Hahnemann Medical College, where he rose rapidly in the ranks from instructor to professor. There, he had major responsibility for psychiatric education and interacted intensely with medical students and psychiatry residents. In addition, he became heavily involved in teaching other physicians as well as other mental health professionals, and these experiences shaped his views of the role of psychiatrists in professional education and as primary care physicians. His interests in education produced a number of important publications related to process as well as content, and he received several awards for excellence in teaching, including the Golden Apple Award and the Lindback Award. The excellent and inspirational quality of his verbal presentations was reflected by his being named Class Day Speaker by several medical student classes. He also was pivotal in founding the Association for Academic Psychiatry, an organization dedicated to psychiatric education, and was one of its first presidents.

From 1972 to 1976 Paul Fink was Professor and Chairman of the Department of Psychiatry and Behavioral Sciences at Eastern Virginia Medical School. During that period he also served as Psychiatrist-in-Chief of the Eastern Virginia Medical Authority and Medical Director of the Norfolk, Virginia, Community Mental Health Center.

His return home to Philadelphia in 1976, as Professor and Chairman, Department of Psychiatry and Human Behavior, Jefferson Medical College, was marked by an expansion of his activities in the national scene. He rapidly moved to positions of leadership in the American Association of Chairmen of Departments of Psychiatry, joining the Executive Council and becoming president. He also served several terms as that association's representative to the Council of Academic Societies of the Association of American Medical Colleges, serving as an advocate for psychiatry, supporting funding by the Alcohol, Drug Abuse, and Mental Health Administration for research, clinical training, and services, and addressing interactions between psychiatry and other medical specialties. He was an especially energetic representative of the APA to the Council of Medical Specialty Societies, initiating collaboration with other medical specialty societies and exhorting the Council to take a more activist role in medical policy affairs.

During this time, Paul Fink became chairperson of the APA Council on Medical Education and Career Development. In this position he used his unique energy and knowledge to bring together colleagues and ideas, leading to much productivity and success. He

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was responsible for the development of a consortium of academic and educational organizations that took leadership in health policy issues as well as substantive educational issues. He was on the Steering Committee of the Educational Development for Psychiatric Educators Project and engaged the APA in efforts to recruit the best medical students. For many years an admirer of Paul Fink's, I had the good fortune during this time to become a close colleague, benefiting from his creativity and leadership in shaping new directions for the APA in psychiatric education. Although at times we argued and struggled, we also laughed and created. The resulting partnership and fine tuning demonstrated the best in collaboration, and it led to a plethora of successful activities.

He became a senior examiner for the American Board of Psychiatry and Neurology; his awareness of candidates' deficiencies made him a crusader for quality in residency training and led to his appointment to the Residency Review Committee for Psychiatry. There, he has been a vocal advocate for excellence and the development of standards to strengthen residency training.

Paul's proposal to the American College of Psychiatrists to develop a standardized, quality residency curriculum and evaluative process led to the formation in 1977 of the Psychiatry Residents in Training Examination—a program that he shepherded through its initial development and for which he received the 1988 Bowis Award, given in official recognition of his outstanding contributions and leadership in the College. More to the point, the Psychiatry Residents in Training Examination has had an enormous influence on residents and their training programs.

The APA, which has also recognized Paul's outstanding contributions to medical education, presented him with the Seymour D. Vestermark Memorial Award in 1982. His Vestermark lecture on stigma broke ground for an examination of the stigma faced not only by persons with mental disorders but by their caretakers as well, and his battle cry for action and vigorous leadership started the process of eradicating the terrible stigma associated with mental disorders (1). His energetic and thoughtful leadership of the APA Joint Commission on Public Affairs initiated our highly effective campaign against stigma and paved the way for the current "Let's Talk About Mental Illness" campaign.

Paul Fink is noted for being able to bring together the best of the many facets and functions of psychiatry. His attention to internal and external liaison has produced better models of collaboration and interaction. He has been a leader in the academic community, and his efforts have brought academicians face to face with members of the advocacy and consumer groups, forcing each to listen respectfully to the other. Through his energy and awareness, a coalition has been forged that is far greater than the sum of its parts and that helps both patients and the profession.

His many successes extend beyond psychiatry. He has been an ardent supporter of the Joint Commission on Inter-Professional Affairs, valuing collaboration and negotiations with other mental health professionals. He has been very active in the Pennsylvania Medical Society, where he has been involved in manpower activities, medical practice activities, and the impaired physician program. Similarly, he has held many positions in the Philadelphia County Medical Society, including the chairmanship of the standing Committee on Medical Economics (to which he was elected), and he was a member of the committees on medical education and long range planning, the Subcommittee on Mental Health, and the Benjamin Rush Award Committee. This year, he was elected President-Elect, and his presidential term there begins as his term at the APA ends. Thus, we see him moving to new fields to conquer.

Paul Fink is a passionate proponent of psychiatry and speaks tirelessly on its behalf, whether it be for higher standards of care in practice, for stricter standards of residency training, or to combat misleading stereotypes regarding the field and its work. Paul is a superb and inspiring author of scientific articles on such topics as creative arts therapy, psychoanalysis, and human sexuality, and his papers have a uniting thread of humanism and caring, as well as the best of scientific medicine. His carefully crafted work on the use of art therapy documents not only his interest in the therapeutic process but also his understanding of art as a reflection of psychological functioning. A lover of music and a devotee of opera, he is not only an appreciative observer but also an active student of language, literature, and the combinations of music and emotion that make this wonderful drama so effective and meaningful.

All of the foregoing provides information about Paul Fink that would be found in the standard curriculum vitae. A more three-dimensional portrait would describe him not only as a scholarly psychiatrist but also as a humanist and a personal friend. This biography would not be complete without mention of Paul's strong network of family, friends, and colleagues.

In 1956 Paul married his childhood sweetheart, Shirley. The relationship was strong and fulfilling. Their early years revolved around family, especially their three sons, David, Mark, and Gary. When the boys were well on their way to adulthood, Shirley went back to school and obtained a Ph.D. in clinical psychology. Paul had much pride in and respect for her clinical acumen and cherishes the many warm letters sent by patients in response to Shirley's tragic death from cancer in 1986.

A loving and caring father, he has delighted in his sons' successes. His special pleasure at David's choice of psychiatry as a career reflects his optimism and excitement at the directions of the field. Equally obvious is his pleasure in Sophie, granddaughter extraordinaire, named in loving memory of Shirley; she and her parents, David and Heidi, are frequent visitors. He is equally proud of Gary's and Mark's many accomplishments and is anticipating with pleasure the marriage of Gary and Christina. To know his mother, Essie Fischler, is to have a preview of Paul in the years to come. Her energy and enthusiasm, optimism, and passion have not diminished over time, and she, too, is an inspiration to others.

Paul's friends grieved with him during Shirley's illness and death. In addition to experiencing great sadness and loss, Paul developed a special understanding of what patients and families face in dealing with serious illness. This insight has expressed itself in redoubled attention to a more sensitive application of psychosocial concepts in patient care.

How wonderful it was to see love and joie de vivre return and to rejoice at Paul's marriage to Phyllis—Peppy—2 years ago and delight in their obvious affection and happiness.

While proud of his family and of his accomplishments, he is remarkably humble, maintains an almost childlike wonder and pleasure at life, and does not fall prey to the self-serving or grandiosity that can seduce leaders. His availability to all—past presidents, residents, medical students, and patients and their families—is legendary.

Paul's energy and humor, wit, and warmth enable him to address difficult problems without becoming polarized. At the same time, his relentless pursuit of goals has made him one of the most productive leaders of this Association. He never demands more than he is willing to do himself. Highly creative and productive, he is impatient with bureaucracy and rules and eager to fix problems. Many leaders surround themselves with a coterie of advisors who soothe, flatter, and protect them from everyday routine and problems. Paul Fink has been a leader of the people, has been responsive to critiques, and encourages others through his President's column in each issue of *Psychiatric News* to respond to his ideas, hopes, and challenges. He has never been too busy to listen to each member who calls or writes and often has turned heaven and earth, or at least APA staff support structure, to ensure a prompt response to each concern or suggestion.

In his Response to the Presidential Address in 1988 (2), Paul noted the importance of interweaving the human aspects of medical care in the applications of biomedical science. His endeavors to combine the scientific and humane will lead to a new biopsychosocial paradigm that truly can overcome stigma.

I have been fortunate to have such a warm and caring, giving and yet demanding friend to whom I could turn for personal as well as professional direction and assistance. Even more so, the APA has been fortunate in having his energetic, passionate, and committed leadership. We will enjoy the fruits of his marvelous accomplishments for many years to come.

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Oscillations of Attachment in Borderline Personality Disorder

Frederick T. Melges, M.D., and Marvin S. Swartz, M.D.

The authors propose that oscillations of attachment in borderline personality disorder stem from a central problem with regulation of interpersonal distance. This problem derives from borderline patients' conflicts between fears of abandonment and domination. When they move closer to others, they fear that they will be dominated; when they move away, they fear that they will be abandoned. Whichever direction they move, they experience negative feedback. This gives rise to recurrent oscillations between attachment to and detachment from others. Because the oscillations are reinforced by the ambivalent reactions of significant others and the involvement of third parties, family therapy is often indicated.

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> A number of porcupines huddled together for warmth on a cold day in winter; but, as they began to prick one another with their quills, they were obliged to disperse. However the cold drove them together again, when just the same thing happened. At last, after many turns of huddling and dispersing, they discovered that they would be best off by remaining at a little distance from one another.
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> —Arthur Schopenhauer (1, p. 226)

Schopenhauer's metaphor of the porcupines provides a useful perspective for the prickly and sticky interpersonal attachments of patients with borderline personality disorder. These patients are characterized by intense interpersonal relationships that vacillate between loving and hating. Although Kernberg (2) and some other psychodynamically oriented theorists see these vacillations as a function of reliance on primitive ego defenses such as intrapsychic splitting, Gunderson (3) also highlights the role of interpersonal processes. While the swings in attachment may well be understood at either the intrapsychic or interpersonal level, we will focus on the interpersonal issues. The patient's stormy relationships are often bewildering to family members (4, 5). In order to provide a framework that may be useful for the understanding and family treatment of these disturbed relationships, we propose a cybernetic model of the oscillations of attachment in borderline patients. We do not intend to preempt other models or levels of explanation but propose the present model as a useful conceptual framework to work with and with which to educate borderline patients and their families.

Our central thesis is that the borderline patient's stormy relationships reflect an underlying problem with distance regulation. We propose that a basic interpersonal problem is that, whether the patient moves closer to or away from other people, he or she experiences negative feedback. This prompts the patient to oscillate between attachment and disengagement.

The problem with distance regulation will be presented in separate sections below as it relates to conflict between opposing fears, interpersonal spirals, and triangulation. Before describing these components of our model, we will provide some definitions and outline our conceptual framework.

CONCEPTUAL FRAMEWORK AND DEFINITIONS

Distance regulation refers to the process of controlling emotional space between people. It is a unifying theme that can explain much about interpersonal behavior in groups and families (6). It pertains not just to spatial distance between people but also to emotional attachment or disengagement. Problems with emo-

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tional attachment, such as overcompliance alternating with angry rebellion or idealization switching to devaluation of others, are common in the empirical studies of borderline personality disorder (3, 7, 8). This discussion will be limited to the empirical definition of borderline personality disorder and to the so-called psychogenic type that remains after other predominant diagnoses (e.g., chronic major depression) have been ruled out (8). Because the majority of these patients are women, we will use feminine pronouns to refer to the patient.

The term "cybernetic" refers to processes of control governed by feedback of information. Negative feedback is information that indicates a deviation from a goal. When these deviations are counteracted, control is achieved (9). Lack of control commonly occurs in two situations. First, it takes place when deviations cannot be counteracted because of a conflict between goals. For example, this occurs in an approach-avoidance conflict—oscillations in behavior occur because approaching produces deviations from the goal of avoidance, and avoidance produces deviations from the goal of approach. Second, lack of control occurs when deviations are amplified by other deviations so that a vicious cycle or spiral occurs. For example, blaming from one partner frequently evokes retaliation from the other, which then escalates the initiator's blaming. The attempted correction amplifies the original problem. Both forms of lack of control—lack of deviation counteraction and deviation amplification—are common in psychopathology (10). Our present task is to describe the specific nature of this lack of control of interpersonal distance regulation in borderline personality disorder.

CONFLICT BETWEEN FEARS AND RESULTANT OSCILLATIONS

As will be outlined later, the main predisposing factor to the patient's problems with regulating interpersonal distance is the conflict between fears of abandonment and fears of domination. Probably because of individual and family difficulties with separation and individuation, the patient fears she will be abandoned if she grows up and becomes independent of her family; on the other hand, if the patient stays close and submits to her family's wishes, she fears being dominated.

We propose that these opposing fears give rise to oscillations of attachment in the patient's current interpersonal behavior. Because of this conflict between fears of abandonment and domination, the patient experiences negative feedback whether she attaches to or disengages from others. Because closeness threatens domination, the patient disengages, but as this threatens abandonment and intolerable aloneness, she again tries to attach, which again evokes fears of domination and subsequent attempts to disengage. Whether she moves toward or away from others, it feels wrong. Consequently, the patient repeatedly swings between attachment (e.g., love, clinging, and idealization) and disengagement (e.g., anger, pouting, and devaluation).

In cybernetic terms, the problematic control process for patients with borderline personality disorder is interpersonal distance: Too much or too little is threatening. Between these poles, the patient operates as though possessed of a "narrow set range" for tolerable interpersonal distance. When this narrow set range is exceeded by minor variations in perceived interpersonal distance, the patient experiences negative feedback. Much like the rapid oscillations of a furnace for which the thermostat has been set at a narrow range, the patient oscillates between attachment and disengagement.

The narrow set range of perceived interpersonal distance appears to stem from the opposite pull of two control systems. One control system is centered on preventing abandonment by maintaining closeness to significant others; the other is centered on preventing domination by keeping distance from others. In cybernetic theory, this conflict between two control systems causes the total system to oscillate because "for one system to correct its error, the other system must experience error" (9, p. 254). For oscillations in borderline personality disorder, this means that moving closer to a caregiver carries the threat of being dominated, while moving away carries the threat of abandonment. The attempted solution to one side of the problem becomes the problem for the opposing side.

In this cybernetic framework, if one thinks of unpleasant emotions as "error" signals reflecting the subjective improbability of reaching a goal (10), the patient is recurrently experiencing "error" and unpleasant emotions whether she moves toward or away from others. Consequently, she switches between loving and hating and becomes emotionally labile and unstable.

The patient's emotional instability is probably aggravated by her overconcern with the other person's attitudes toward her, which prompts her to focus almost exclusively on the present (11). In this regard, Lewis (12, p. 1496) states: "The affect associated with the patient's present state is so pervasive that it somehow blots out the memory of previous states with a very different affective tone." This may account for the recurrent exaggeration of the patient's fears.

Although a cybernetic framework has not been used, emotional lability and vacillating attachments have been attributed by some theorists to conflict between opposing fears. For example, Maltzberger and Buie state: "Borderline patients typically are harrowed by a sense of aloneness, and in their relations with others are tortured by alternating horrors of abandonment and engulfment" (13, p. 126). In his review of the literature, Shapiro reports: "They present the manifest conflict of extreme dependence and intense fear of closeness, the solution to which appears to be the constant preoccupation with maintaining the 'proper' distance from the therapist in order to regulate their anxiety about both distance and closeness" (11, p. 1307). This formulation emphasizes the patient's fear of merging with others and not the fear of domination as the opposing pole from distance. Nevertheless, in essence, the patient oscillates between attachment and disengagement because in whichever direction she moves she experiences negative feedback.

INTERPERSONAL SPIRALS

As a result of the patient's difficulties with distance regulation and her confusing affiliative behavior, significant others often become perplexed, frustrated, and ambivalent about her (4, 5). This feedback confirms her anxiety about being abandoned, which prompts her to cling even more to them. This increases their ambivalence and perhaps even induces them to distance themselves, which reinforces her fears of being alone. When significant others, such as a spouse or caregiver, actually disengage, the patient's fear that she will be abandoned materializes as a result of a self-defeating spiral created by her own desperate attempts to prevent being alone (14). This spiral appears to be amplified by the borderline patient's anticomplementary interpersonal behavior that is at odds with usual social expectations. Normally, the other person expects that as the patient moves closer, he should complement the move by becoming friendlier; similarly, as she moves away, his expectation is to reciprocally disengage (15). But these normal complementary reactions of the other person produce anticomplementary attachment behaviors in the borderline patient by evoking her fears of domination or abandonment. As he moves closer, she fears being dominated and moves away; as he moves away, she fears abandonment and moves closer.

This switching of the interpersonal axis of closeness-distance to that of domination-submission generates mismatched social expectations, which can also be understood as intrapsychic splitting. From an interpersonal viewpoint, the apparent intrapsychic splitting is most evident when the other's complementary movement toward closeness suddenly evokes hostility instead of the expected complementary friendliness. These switches could also be understood at the intrapsychic level as splitting and projective identification. Projective identification has a considerable interpersonal component in that the other person may unconsciously comply with the patient's projected image of being abandoned or dominated. That is, the patient's expectations may elicit actual distancing or control from the other person, who may unconsciously collude with what the patient expects (14). In addition, the collusion of third parties commonly plays a role in the interpersonal rifts between the patient and a significant other.

TRIANGULATION AND STABILIZATION OF DISTANCE REGULATION

We propose that the borderline patient's oscillations and interpersonal spirals are often partially stabilized by triangular patterns between people. According to Bowen (16), when tension arises between two people, it is often diffused by involving a third party. For borderline patients, such triangulation of a third party is common in their families and is often recapitulated on psychiatric inpatient units. It enables the patient to regulate her distance from others so that they become neither too close nor too disengaged.

Triangulation often is precipitated by the borderline patient feeling victimized in part because she experiences other people as having the power to abandon or dominate her. When victimized, the patient feels entitled to be cared for and rescued. When she is not rescued by a caregiver, she often turns to third parties to seek a rescue. Her often entitled demands for care and nurturance prompt these third parties to either rescue or reject her. Commonly, the rescuers and rejecters become pitted against one another: The rescuers view the patient as helpless, whereas the rejecters see her as manipulative and abrogating responsibility for herself (3, 17). What ensues is an actual multiperson split between the rescuers and rejecters, with the patient as a victim in the middle of the split camps.

This triangular interaction between rescuer, rejecter, and victim—called the drama triangle by Karpman (18)—often serves as a framework in which the borderline patient can regulate her distance from others. As the victim in the middle, she maintains some distance from the rescuer when his or her nurturance is criticized by the rejecter, and yet she also remains connected to the rejecter when the rescuer saves her from being totally rejected by him or her. In effect, the rescuer and the rejecter cancel each other out as the victim maintains her tolerable amount of distance from each of them.

In essence, triangulation permits the borderline patient to regulate her distance from others so that her dyadic oscillations recur but do not become extreme. Both the patient and the system become "stably unstable" (19). While instability is manifest in the patient's dyadic relationships, the overall triangular distance regulation remains stable. This stabilization restores a semblance of control to the patient's relationships and thereby makes the triadic entanglements resistant to change. This perspective also implies that, so long as triangulation exists, the dyadic oscillations will continue.

ETIOLOGICAL CONSIDERATIONS

Although detailed discussion of the biopsychosocial factors that may give rise to the borderline patient's oscillations from fears of abandonment and domination are beyond the scope of this paper, we will mention some developmental hypotheses relevant to our model. From a biological standpoint, the impaired auditory processing of these patients, found by Kutcher et al. (20), may make them vulnerable to overreacting to stimulus complexity and may account, in part, for the observation that they lose perspective and become consumed by present emotions (10). At the psychological level of inquiry, many psychoanalytic writers (2, 21–23) have highlighted the patient's problems with separation-individuation from a nonempathic and domineering mother. The introject of the mother as both an abandoning and controlling image could condition the patient's simultaneous fears of abandonment and domination.

From a social-family perspective, Bowlby (24, 25) argues that early patterns of attachment play an enduring role in personality disturbance. Arguing that early attachments serve basic survival, he further posits a CNS cybernetic system that serves to maintain closeness with partners and is patterned after early dyadic bonds. Early salutory attachments also provide a secure base from which early childhood exploration can begin, with the secure base facilitating exploratory autonomous strivings, which are antithetic to attachment. The cybernetic system, an attachment control system, maintains an individual's relationships to his or her attachment figure within a range of distance and accessibility, allowing attachment and exploration to occur. Bowlby sees the basis for an adequate control system in the "secure attachment" paradigm studied in mother-child dyads by Ainsworth et al. (26–28). This pattern of attachment instills confidence that the parent is available, responsive, and helpful if problems arise during exploration.

Bowlby has argued that personality disturbance is likely to arise in an alternative pattern of attachment that was also studied by Ainsworth and is termed "anxious resistant attachment" (26–28). In this pattern the parent's availability, responsiveness, or helpfulness is uncertain and results in separation anxiety in the child. This pattern is seen by Bowlby when a parent uses threats of abandonment as a means of control and results in anxious and ambivalent attachment to the parent or other attachment figure. Hence, oscillations in attachment may result from early anxious, resistant attachment.

Zinner and Shapiro (29) and Berkowitz (30, 31) have also examined the family perspective in their work on borderline adolescents. They view the problematic family environment as a failure to provide an adequate holding environment during phase-appropriate recapitulation of separation-individuation in adolescence. Thus, rather than tolerate the often trying demands and tribulations of the adolescent period, the family group of the borderline adolescent regresses in group functioning. Distinctions in boundaries between individuals become blurred, primitive ego defenses are activated, and, in particular, disavowed aspects of the parent are projected onto the adolescent or other family members. Thus, under the stress of the adolescent strivings, internalized conflicts in the parents are often externalized and manifest in interpersonal conflicts within the family. Therefore, the borderline patient's pathological intrapsychic defenses, such as splitting and projective identification, actually are patterned after conflicts *between* individual family members.

Viewed by these authors, a common pattern of family regression during the adolescent separation period is counter-separation behavior. That is, the parents thwart separation and individuation by using threats of abandonment or withdrawal of love when the child tries to grow up and become independent of the family. If the patient remains "in" the family, she is good; if she attempts to "move" out of their control, she is bad. Such a bind is apt to produce the simultaneous fears of abandonment and domination and induced oscillations of attachment seen in borderline patients.

In a study that compared biopsychosocial developmental hypotheses, Soloff and Millward (32) found stronger evidence to support family pathology in the etiology of borderline personality disorder. Although there are variants of neglect and control, the usual pattern is for the father to be underinvolved with the patient, while the mother is markedly overinvolved, negative, and intrusive. Clinically, we have found that the mother's enmeshment with the daughter often has been spurred by the mother's depression or unresolved grief, which inhibited the child's aggression and individuation (33). The mother tried to care for herself by projecting her own dependency needs onto the patient and binding the child to her with threats of abandonment should the child grow up and become autonomous (29). In a family in which the child is dominated by threats of abandonment, the child will likely become preoccupied with keeping the right amount of distance from others.

CASE REPORTS

Case 1. Ms. A, a single woman with borderline personality disorder, was admitted to the hospital after a suicide gesture. She had been doing reasonably well, having been employed for several weeks in a job that she did not enjoy but tolerated. She had found in her job and relationships outside work that she could do best by keeping relationships fairly structured and superficial. She kept her parents at a distance and refused treatment efforts that involved her parents. Most friendships were limited to evening classes in which she enrolled. Ms. A often complained of loneliness and emptiness but observed that "getting involved" with men or women was worse because she felt that she was only likable if she maintained a quiet and submissive role in these relationships, which inevitably enraged her. Recently a man began seeking her company, and because of his persistence and her loneliness she acceded. He eventually made it clear that he desired a romantic relationship, which she reluctantly agreed to. Ms. A felt anxious and oppressed by the relationship. She had a recurrent thought that he could control her. She became preoccupied with guilt and a sense of badness, in part because she felt she had submitted to him to fend off her loneliness. She felt revolted by herself and made a suicide gesture.

Case 2. Ms. B, a married woman with borderline personality disorder, was admitted to the hospital after a suicide attempt precipitated by a confrontation with her husband about his alcohol abuse. Earlier that day, Ms. B had sought solace from her parents about her marital discord. Her parents suggested a separation and that Ms. B move home. Feeling trapped by the desire to return home and fear of returning home, Ms. B took an overdose. Once hospitalized, she described an intense desire to be close to her husband. She often fantasized about a quiet, harmonious home life. Paradoxically, she felt very anxious when she actually felt close to him. At those times she became fearful that he was going to take advantage of her either by failing to contribute to their financial responsibilities or by seeking out other female relationships. In fact, often when she felt most loving toward him, she had recurrent fantasies of his unfaithfulness. At these times she would seek out and present evidence of his imagined infidelity, which precipitated a confused and angry response from her husband. She took his anger as confirmation that he did not understand or care about her. The disputes between the couple were often reported by Ms. B to her parents, who took their daughter's side. They had been skeptical about the marriage from the start and found it difficult to tolerate Ms. B's ambivalence about her marriage. They often tried to intervene to resolve her ambivalence in favor of separation.

The inpatient treatment approach attempted to address both the extreme oscillations in the marriage and the triangular involvement of the parents. The parents were enjoined to distance themselves from their daughter's marital difficulties until the marriage was stabilized and were offered supportive treatment, primarily to help them with their anxieties about their daughter. Treatment with Ms. B. focused on her difficulties with finding the proper distance in relationships and the way in which her oscillations affected other members of the family. This theme was used in marital and individual work, with an initial emphasis on both partners learning to tolerate unpleasant feelings stirred up by fears of aloneness and submission rather than acting upon them. More intensive family work was anticipated once the marital relationship was on a better footing.

TREATMENT IMPLICATIONS

If the proposed model is correct, in order to dampen the oscillations of attachment in borderline personality disorder, the patient and her social network must learn new ways of dealing with regulation of interpersonal distance. Although controversies abound about the optimal form of individual treatment for these difficult patients (3), a family therapy approach (including marital therapy) has been relatively underutilized. Commonly, family members are mystified and exhausted by the patient's unpredictable oscillations of attachment (4, 5). Bringing the family together to discuss problems with distance regulation in a psychoeducational approach can be an important first step toward diminishing the oscillations.

By making explicit the patient's covert fears of abandonment and domination, the oscillations in attachment behaviors can be empathically anticipated and sometimes prevented. Prevention of these oscillations is most readily accomplished by attending to early signs of the patient's anxieties and rehearsing how to verbalize and negotiate the felt need for distance rather than allowing the usual distancing or clinging behaviors to effect distance from others. If nothing else, this type of approach provides a nonpejorative context for family members to understand their shared problems. By reducing inference about unconscious motivation, it may also provide an easier conceptual framework for families to work with.

The next step in treatment is to dismantle triadic entanglements because these appear to perpetuate the patient's oscillations. The goal is to change triangular distance regulation into dyadic problem solving. Often this entails having each party take a firm stand against allowing the other to wield power by emotional displays or threats. Triangulation commonly occurs between the patient, mother, and father or husband. Usually the father or husband needs to be taught to refrain from rescuing the patient or mother and to calmly remove himself from the fray between them.

Because the extreme oscillations often center on the patient's relationship with her mother or substitute mother figures, this is often a key issue for family therapy. It is common for the patient and mother to be intensely ambivalent toward each other and highly enmeshed. Usually each feels hurt, exhausted, and unappreciated by the other. The goal is to modify the intensity of the relationship so that it is more casual, tender, and mutually supportive. Initially, it is important to empathize with the mother's unavoidable hardships of her past, such as unresolved grief or depression, that propelled her to become embroiled with her daughter. This understanding fosters mutual empathy between the mother and daughter. They can then be asked what they would like to change in their present relationship. The therapist reinforces mutual support but points out the difficulties they encounter with expectations of total love or intrusiveness. Once they feel mutually supported, they are then encouraged to examine past binds and distorted expectations. Later, future scenarios that are different from these expectations can be envisioned and rehearsed.

This recalibration of a reasonably soothing yet differentiated mother-daughter relationship usually has considerable impact for mollifying the patient's oscillations not only with her own mother but also with other important relationships. Both daughter and mother often come to feel that the other is an ally rather than an enemy. Research has shown that conjoint sessions between borderline patients and their mothers are highly productive and, on psychological tests, has shown that they substantially reduce the patient's primitive defenses (34). Through family therapy, borderline patients and their families over time may acquire enough social learning so that, like Schopenhauer's fable of the porcupines, they discover that "they would be best off by remaining at a little distance from one another."

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CONCLUSIONS

Although not all of the psychopathological manifestations of borderline personality disorder can be explained on the basis of the proposed problem with regulating social distance, we believe that, at least at the interpersonal level, this cybernetic model provides a unifying framework for understanding the borderline patient's opposite swings of attachment behavior. In essence, we propose that borderline personality disorder is an oscillatory disorder and that the oscillations of attachment stem from recurrent negative feedback about optimal interpersonal distance.

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Quality Assurance Monitoring in Psychiatry

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The implementation of quality assurance monitoring is an important response to public demands for accountability in medicine as well as a requirement for institutional accreditation by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). The author examines the somewhat elusive definition of quality as it is applied to medical care. He reviews the history, terminology, and reasons for quality assurance monitoring and presents the JCAHO-defined concepts of indicators and thresholds. Several common problems associated with the implementation of quality assurance monitoring are discussed along with guidelines for the development of quality assurance indicators in psychiatry.

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The search for quality in medicine is like the search for the perfect mother: approximations are found, the search continues, and hope endures. Realistically, the defining characteristics of medical quality change continually. Often they depend on when and how care is evaluated (1, 2). Today's quality may be tomorrow's negligence. In *The Principles and Practice of Medicine,* Sir William Osler (3) described the following medical treatment for diabetes: "Opium alone stands the test of experience as a remedy capable of limiting the progress of the disease" (p. 304). Needless to say, a similar treatment today would be considered malpractice. This paper will examine the concept of quality in medicine and discuss the process of monitoring medical care, including psychiatric care, to ensure that it meets predefined standards of quality. As we shall see, quality is easy to define in the general sense but difficult to pin down in a specific sense. Some of the reasons for this difficulty will be discussed, and suggestions will be made that should help in the implementation of quality assurance monitoring programs in psychiatry.

BRIEF OVERVIEW OF QUALITY ASSURANCE POLICY

The goal of quality assurance is to ensure that the important aspects of medical care are delivered in accordance with preestablished standards of acceptable medical practice (4–6). Early attempts at quality assessment started spontaneously in the first quarter of this century and continued into the 1950s (7, 8). In the last few decades the high cost of medical care, the rise of consumerism, and the health rights movement have placed increasing pressure on the medical care system for accountability (9–11). The federal government and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) (formerly the Joint Commission on Accreditation of Hospitals, or JCAH) have been the two major institutional forces behind quality assurance since the 1960s. The government's initial involvement in quality assurance arose from its increasing concern about cost containment, effective utilization of resources, and the quality of care provided in federally funded medical programs such as Medicare, Medicaid, and maternal and child health programs. JCAHO is a private group that has been mainly concerned with the development and application of professional standards of quality medical care since its formation by several independent professional medical associations in the early 1950s. Accreditation surveys by JCAHO are requested by hospitals and other health care groups. Approval by JCAHO "deems" hospitals, that is to say, makes them eligible for reimbursement for most federally funded medical programs and third-party payments.

Federal health care legislation passed in the mid-1960s required that institutions participating in the Medicare and Medicaid programs have operational utilization review plans. These cost-containing efforts were generally ineffective in controlling the unnecessary use of medical facilities. In response, Congress enacted the 1972 Social Security Act, which established the professional standards review organizations (PSRO) program (12). One main emphasis of the program was to determine whether the services provided were necessary, of acceptable quality, and delivered in an appropriate fashion when measured against explicit criteria of care (7). Several types of studies were performed to assess care, including concurrent review of individual cases, profile analyses, and clinical care evaluation studies. However, opponents argued that the professional standards review organizations were

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spending more money than they were saving (13). In response, Congress passed the 1982 Tax Equity and Fiscal Responsibility Act, which set up peer review organizations (PROs). Peer review organizations are structured differently from professional standards review organizations and function primarily to contain costs and ensure the quality of federally financed medical care (14, 15). They gained more power over health care providers under the Sixth Omnibus Budget Reconciliation Act of 1984 and the Comprehensive Omnibus Budget Reconciliation Act of 1986.

Federal guidelines for quality assurance in community mental health centers (CMHCs) were mandated in the Community Mental Health Centers Amendment of 1975 (Public Law 94-63) and the Mental Health Systems Act of 1980 (Public Law 96-398). In response, both the National Institute of Mental Health and JCAHO developed model CMHC quality assurance programs (16). Although both laws were subsequently repealed, CMHCs are still required to conduct multidisciplinary quality assurance reviews (7, 17–19).

In the 1960s and early 1970s, JCAHO formulated quality assurance guidelines that encompassed the requirements for Medicaid and Medicare qualification. By 1972, JCAHO had developed a system of required chart audits, consisting of complicated diagnosis-related studies of relatively large numbers of patients (20). Despite the expenditure of large amounts of time and money, the audits apparently did little to improve the quality of patient care. Audits were often performed in a mechanical way, mainly to fulfill the JCAHO requirements rather than to investigate important problem areas in medical care. Therefore, in 1979 the audit requirement was discontinued. In the early 1980s, JCAHO introduced a new multistage quality assurance program that emphasized the identification of important medical care measures and problems followed by the monitoring of the measures to determine whether they met preestablished criteria and standards of care (9). Basically, JCAHO asked whether the institution had the capacity to provide quality medical care. This approach became official JCAHO policy in 1985 in the *Accreditation Manual for Hospitals* (21, 22).

In 1987, JCAHO initiated a new quality assurance drive called the "Agenda for Change" (11, 23, 24). This new approach was partially motivated by the repeated difficulty that clinical professionals were having in identifying and monitoring critical elements of medical care (25). The new approach focuses on the development and use of a standardized set of severity-adjusted clinical indicators to identify and monitor high-volume, high-risk, or problematic areas of clinical practice. The emphasis is on clinical outcome rather than the delivery of care. JCAHO now asks whether the organization actually provides quality care rather than whether it has the capacity to provide quality care. Health care organizations are required to send the results of quality assurance monitoring to JCAHO on a continuing basis. This approach is consistent with the main trend in quality assurance during the past 20 years away from large, time-consuming, mainly retrospective medical record audits to rapid, flexible monitoring of important variables related to the outcome of care.

The current emphasis on quality programs can best be viewed as a response to several important changes in medicine and in our society as a whole (26, 27). The increasing complexity and specialization of modern medical treatment often require specialty training and lead to demands for official certification as a proof of competence. The increasing cost of medical care in a time of economic stress has led third-party payers and consumers to demand that services be provided in an effective and cost-efficient manner. The rise of the consumer movement has led to a demand for greater accountability in medicine as well as other commercial services. This movement is accompanied by increasingly costly litigation for perceived and actual errors of judgment. These and other social forces have led to a climate of increasing monitoring of medical care and demands for quality and accountability.

NORMS, CRITERIA, AND STANDARDS

The quality assurance process has its own specific terminology that is often confusing. The traditional conceptual terms include "norms," "criteria," and "standards." Norms are measures of the actual clinical practice of health care professionals—statistical summaries of large numbers of patients without any implied judgment of the appropriateness of care. The average amount of a tricyclic antidepressant medication prescribed to patients with a diagnosis of major depressive episode would be an example of a clinical norm in psychiatry. Criteria are statements that define appropriate clinical care. They serve as yardsticks or bench marks against which the actual clinical care can be measured (28–30). Criteria are determined by professionals on the basis of their clinical experience and the current scientific literature. A quantitatively defined criterion for the pharmacological treatment of depression might state that patients with a diagnosis of a major depressive episode should be given a trial treatment with 100–200 mg of a tricyclic antidepressant such as imipramine. Some authorities have argued that a criterion should be more qualitative and that the quantitative specification (i.e., dose range) should be provided by a separate standard of care (28). This method is confusing because it fragments the guidelines of care between two separate entities—criterion and standard. The approach I favor is to provide quantitative information in the criteria, where it seems natural and appropriate. For example, a criterion that a serum level of 0.8–1.0 meq/liter of lithium is the maintenance lithium blood level for a patient with a diagnosis of bipolar disorder is preferable to saying that such a patient should have a lithium blood level in the therapeutic range.

Criteria can be classified in several other ways (29, 30). Criteria based on the assessment approach may describe the structure, process, or outcome of quality care. Structure refers to the physical, organizational, and technological resources of the care provider. Process describes how the care is provided to the patient. Outcome describes the results of the care. For example, the availability of a modern, correctly functioning ECT machine would be related to the structure of care. The correct administration of ECT and the subsequent resolution of the depression would be elements of the process and outcome of care, respectively.

Criteria can also be classified as implicit or explicit, based on whether they have been prespecified. Implicit criteria depend on the assessment of the quality of care by one or more expert professionals on the basis of their clinical experience. There are no detailed guidelines stipulated in advance. Explicit criteria are clearly specified before any assessment is made. A group of experts carefully develops written criteria that can then be applied by personnel with far less training. Clinical supervision is an example of the use of implicit criteria in psychiatry. Explicit criteria in psychiatry are provided by official diagnostic systems such as *DSM-III-R* and by APA's *Manual of Psychiatric Peer Review* (31).

Criteria can also be described by their referents. A referent is the condition, problem, diagnosis, or treatment to which the criteria apply. Criteria for the identification of specific psychiatric disorders would be diagnosis-referenced, those associated with patient violence would be condition-referenced, and those pertaining to ECT would be treatment-referenced.

Finally, criteria can be categorized according to their source. Normatively derived criteria are recommendations for care based on the judgments of a group of expert clinicians. Empirically derived criteria are based on a survey of what is actually being done by a group of professionals or a specific health care institution.

Standards are sometimes considered to be quantitative specifications of a criterion in a form that clearly stipulates what is acceptable practice (28, 30). JCAHO tends to use the word "standard" in a generic sense to mean the expected or required level of care—usually the level of care that follows the specific criterion all of the time. However, in many cases it would be unrealistic to expect 100% compliance. Therefore, frequently a value less than 100% has been stipulated for the standard of care to take into account unavoidable problems in complying with the criterion. This twofold use of the concept of a standard has produced some confusion in the past. To clarify this problem JCAHO introduced the concept of a threshold, which will be discussed further. In this paper I will use the JCAHO generic notion of a standard.

INDICATORS AND THRESHOLDS

The concept of a medical indicator is not new. Chambers et al. (32) defined an indicator condition as a frequent, treatable clinical situation that often encompassed several criteria. Lane and Kelman (33) developed a large number of indicators for pregnancy; however, most of these indicators were general statements of clinical goals rather than quantifiable measures of care or outcome. Kessner et al. (34) described the use of tracers representing rather broadly defined identifiable health problems, such as visual disorders or otitis media. Tracers were required to be well-defined but not necessarily easily quantitated. JCAHO (11, 25) uses a more restricted definition for an indicator, describing it as a well-defined, measurable variable related to the provision or outcome of medical care. Indicators, unlike criteria, constitute valueless dimensional variables in the sense that there is no judgment of good or ill intrinsically attached to them, although frequently they measure complications of care. The number of cases of tardive dyskinesia secondary to neuroleptic medication, the number of incidents of physical violence on an inpatient psychiatric service, or the percent of patients responding to a specific dose of a neuroleptic with decreased psychotic agitation would all be considered measurable indicators in psychiatry.

Indicators, as defined by JCAHO, relate to important dimensions of care that are high volume, high risk, or problem prone. They may include or be part of clinical criteria. For example, an indicator that requires measuring blood pressure before and 1 hour after an initial dose of chlorpromazine could also be a criterion. However, an indicator that measures the occurrence of dystonic reactions to neuroleptic medication is simply a quantitative variable that does not imply any standard of care.

Once an indicator is defined, a decision must be made about how to deal with cases that have been identified by using the indicator. Presumably, an investigation should be carried out when a substantial number of such cases are identified. Since resources are limited, it is not possible to investigate every case that is identified for every indicator. There must be some method of customizing each indicator so that it will trigger an investigation at the appropriate time. The threshold, a concept introduced by JCAHO (11, 25) in the "Agenda for Change," serves just such a purpose. A threshold is defined as that preestablished point in the collection of indicator data when an intensive evaluation is triggered to determine whether a problem or opportunity to improve care exists. For example, although patients should not sign out of the hospital against medical advice, a certain number will under the best of circumstances. A hospital department might decide that the discharge against medical advice of up to 5% of its inpatients is tolerable even if the standard of care is that no patients be discharged in this way. Therefore, the threshold for this indicator is 5% or 95%, depending on how the indicator is worded. In other words, as long as only 5% or less of the patients are discharged against medical advice or, conversely, more than 95% of the patients are discharged in a normal way there is no need for further investigation. However, a rate of discharges against medical advice above 5% will trigger further investigation of the problem. For some indicators, such as suicide, the threshold should be set at 100% or 0%, because any suicide is important enough to trigger an inquiry.

Deciding on the threshold level can be a problem because there is no intrinsic reason why the threshold for discharges against medical advice, for example, should be 95% rather than 85% or any other value. Usually the level is set by expert opinion, although Williamson (35) and McAuliffe (36) have suggested that standard statistical criteria be used to determine the appropriate threshold level. Despite this problem, the threshold is a valuable concept because it allows the monitoring process to accommodate the variability that is a part of normal clinical care.

THE DEFINITION OF QUALITY IN MEDICINE AND PSYCHIATRY

Quality medical care is defined by a series of guidelines or standards of care that stipulate how and when a given amount of medical resources should be used to maximize the ratio of health benefit to health risk for the most people. These guidelines are based on expert opinion and empirical studies of the process and outcome of diagnosis and treatment. The general goal of quality assurance monitoring in psychiatry is to identify and correct problems in the diagnosis and treatment of mental illness and ensure that care is provided in accordance with the accepted standards. The monitoring process begins with the identification of important aspects of care. Although most quality assurance monitoring in the past has used measures of process, JCAHO (11, 25) and third-party payers have begun to argue that outcome is the only valid measure of the quality of care. In accordance with this principle, JCAHO (24) has recently developed pilot outcome indicators for obstetrics, anesthesia, and general hospital care. The indicators are well-defined and important dimensions of care that, for the most part, monitor complications in clinical outcome such as low birth weight or cardiac arrest following anesthesia. JCAHO plans to identify indicators in other specialties, including psychiatry, in the near future.

Unfortunately, the use of outcome measures, especially in psychiatry, has certain inherent problems because many variables in addition to the elements of clinical care contribute to the final outcome. As a result, a poor outcome does not necessarily mean that quality care was not provided, since the severity of the illness, age of the patient, and many other factors may have negatively influenced the outcome. These risk factors or covariates must be controlled in any analysis of outcome in order to determine how much of the outcome is explained by the processes of care and how much is due to covariate factors (24, 37).

Some investigators have reported that there is little relationship between the process and outcome of care in specific medical conditions such as hypertension (1, 38). Others have shown evidence to the contrary (39). McAuliffe (40, 41) has extensively reviewed this issue and concluded that there often has been little validation of either outcome or process measures. He stated, "It does not follow that the quality of medical care in any particular case can be defined by whether health was attained" (40, p. 120). McAuliffe (40) concluded that controlled studies are needed to rule out the role of extraneous factors when trying to demonstrate the relationship between the process of care and clinical outcome. Once a strong cause-and-effect relationship has been established, process can be monitored as a surrogate for the outcome of care (28, 29). Despite the uncertainties, third-party payers and JCAHO have clearly indicated that they expect to concentrate on outcome measures of care in the future (11). This does not mean that the process elements of care will be ignored. Rather, institutions will increasingly be expected to monitor process elements of care that have been shown to be directly related to clinical outcome.

THE REASONS FOR QUALITY ASSURANCE MONITORING IN PSYCHIATRY

Health care professionals normally make inferences based on their clinical experience. However, not everyone is equally skilled in the ability to draw correct or useful inferences from clinical data. Sometimes this process leads to the development of idiosyncratic clinical habits that diverge substantially from accepted standards. These clinical habits are often medical examples of the expression of common human cognitive biases or errors in judgment (42–44). Tversky and Kahneman (42, 43) have described how human beings use intuitive heuristics or rules to make decisions and predictions about the likelihood of future events occurring. Often these heuristics lead to errors of judgment. A common error, based on the availability heuristic, occurs when an individual makes an assessment of the probability of an event occurring by the ease with which specific instances of the event can be recalled. For example, "one may assess the risk of heart attack among middle-aged people by recalling such occurrences among one's acquaintances" (42). Similarly, a psychiatrist might assess the effectiveness or danger of a particular medication by recalling striking occurrences when it worked successfully, other situations when the patient experienced a serious side effect, and still other situations when a colleague or publication reported a substantial negative or positive experience with the medication (45). This assessment may ignore many situations when the medication did not work or was used successfully without any side effects because these instances were not as striking or memorable.

Tversky and Kahneman (42, 43) also described another error of judgment, which they called a lingering false belief in the law of small numbers. This belief leads clinicians incorrectly to conclude that small samples are representative of the larger populations from which they are drawn. Therefore, they may consider a published study of a new medication or their own experience with the medication meaningful even though it tests the medication on relatively few patients (46). Chapman and Chapman (44) have studied what they call the problem of illusory correlation in which subjects believe that independent events are connected, especially when there is some subjective verbal association between the events. Their classic study of the Draw a Person Test showed that results claiming an association between drawings of "large and atypical eyes" and paranoid or suspicious traits in the person who drew the pictures were mainly based on the preconceived notions of the examiner. Similarly, a health care professional may describe a patient as paranoid partially on the basis of the observation that his eyes rapidly dart around the room and he appears to be looking at the clinician suspiciously.

Problems occur even when health care professionals do their best to perform their duties according to the accepted standards of care. Accidents, defective equipment, miscommunications, or any of a number of unforeseen complications can interfere with medical care. Subsequent investigation may reveal that the problems have as much to do with administrative decisions as with errors in judgment or deficient training. Quality assurance monitoring can help screen important areas of care to detect many of these problems, thereby reducing the risk for patients and improving care.

QUALITY ASSURANCE MONITORING IN MENTAL HEALTH

Several authors have reported on mental health peer review systems. Edelstien (47) described a program of psychiatric peer review based on a peer review check sheet of important inpatient psychiatric data that was completed by the physician and reviewed by a committee after the patient's discharge. Initial physician cooperation was poor until participation was made a requirement. There was no attempt to formally study the process. Sarnat et al. (48) asked therapists to answer standardized questions on the clinical problems, diagnoses, and clinical outcomes of their psychotherapy patients. Therapists' global ratings of treatment success ranged from 69% to 96%. However, there was no objective third-party evaluation. These authors commented on problems such as difficulty defining the task, staff resistance, and concern over the use of the data. Diamond et al. (49) instituted a peer review system to monitor the prescription of psychotropic medication by psychiatrists in a CMHC. Comparisons of prescription habits before and after establishment of peer review showed a statistically significant drop in polypharmacy and inappropriate administration of antiparkinsonian agents after the institution of peer review. Luft et al. (50) interviewed patients and therapists to examine whether peer review activities interfered with the physician-patient relationship. Most therapists considered feedback from the peer review committee helpful. Patients, however, were concerned about the committee's interference in their treatment. Luft and Newman (51) described a "high-user committee" that conducted intensive peer review of the treatment of difficult, long-term patients. A random, blinded study of an experimental group of patients whose care was reviewed by the committee and a control group of patients whose care was not reviewed showed no differences in outcome or utilization of services between the two groups.

Peer review is often started at the request of third-party payers. The Washington Psychiatric Society Peer Review Committee was established in 1972 to respond to questions by insurance companies about the appropriateness of treatment in the Washington, D.C., area (52). The standards established by the committee were adopted by many local insurance companies, resulting in fewer cases referred for peer review. This represents a good example of professional leadership in the establishment of standards for third-party reimbursement of psychiatric care. A similar but more extensive peer review system was established by the Civilian Health and Medical Program of the Uniformed Services (CHAMPUS) in association with APA and the American Psychological Association (53). However, little attempt has been made to correlate the CHAMPUS review process with outcome of care (54).

Quality assurance monitoring is often used to evaluate multiple components of a clinical service or institution. Linn and Linn (55) have commented on the importance of the multidimensional approach to evaluation in mental health as a model for evaluation of general medical care. Price and Greenwood (56) described the use of an existing comprehensive treatment plan to monitor the quality of care provided to adolescents in a residential treatment center. They reported that use of the plan resulted in staff taking treatment plans very seriously. Unfortunately, they provided no data showing the effectiveness of the monitoring system, nor did they show whether concern for the treatment plan was reflected in a substantial, measurable improvement in the quality of care.

A similar problem exists in the quality assurance monitoring systems reported by several other authors who made little attempt to evaluate the effectiveness of the quality assurance process (57–60). Silverman et al. (61) conducted a year-long retrospective study of the effectiveness of peer review treatment recommendations made for problem cases. Although only 14% of the cases required a second review and 88% of the suggestions made by the review committee were implemented, there was no attempt to measure the actual effect of recommendations on patient care other than to suggest that the low rate of second review indicated their effectiveness.

JCAHO and others (11, 24, 62) have recently emphasized the importance of outcome monitoring. In response, Stevenson et al. (63) established an extensive psychiatric inpatient admission and postdischarge monitoring system. Implementation problems included complaints of intrusion on the treatment of the patient, higher than expected cost, and a longer than expected time required to interview each patient. However, postdischarge results demonstrated a statistically significant global improvement as well as specific improvements in mood and overt behavior.

Many mental health quality assurance monitoring systems are notable for their lack of an empirical basis for the selection of the clinical factors to be monitored. Furthermore, they rarely include any provision for determining the effect of the monitoring itself on the outcome of clinical care. Although most authors have reported a positive effect of their system, the reports are usually anecdotal and impressionistic. In some instances controlled studies of the effect of monitoring have been unable to demonstrate any significant positive effect produced by the monitoring and intervention (50). In addition, the quality assurance process sometimes can become an end in itself if staff are judged by how efficiently they complete long and sometimes complicated monitoring forms. Monitoring a large number of clinical measures does not necessarily lead to better care. Reports of successful monitoring programs that have led to changes in the actual provision of care often have a specific and limited goal, use clearly defined and validated assessment instruments, and contain a clear statement of the standards of care (49, 63, 64).

IMPLEMENTING QUALITY ASSURANCE MONITORING IN PSYCHIATRY

The initial step in developing a quality assurance system is the assignment of responsibility to those individuals who will determine standards of care and oversee the monitoring process (11, 23–25). JCAHO has acknowledged that the quality assurance monitoring process is complex and that determining what to monitor and how to monitor it has been a difficult task for many clinicians (25, 65). Individuals selected to organize quality assurance activities may require additional training and certainly will have to spend a substantial amount of time learning about the quality assurance process and how it should be implemented. A multidisciplinary quality assurance committee often provides a wider perspective on clinical care than a group composed of professionals in mainly one discipline. The committee must be invested with some authority to review care and enforce compliance with standards. Without this authority the quality assurance process becomes at most an academic exercise.

Identifying Important Aspects of Care

The identification of clinical problems or aspects of care to monitor is one of the most difficult steps in the quality assurance process (23, 30). The aspects of care selected for review should, if possible, be related to clinical outcome and preferably represent high-volume, high-risk, or problematic areas of clinical practice. It is appropriate to monitor process elements of care if there is empirical evidence that they have a demonstrable impact on the outcome of care. Williamson (35) has recommended focusing on "those factors which might have the greatest probability of effecting significant improvement in the health status of a target population." The study of the recognition and diagnosis of depression in the emergency department by Kass et al. (66) is an example of such a focus. Brook and Lohr (67) suggested that problem identification activities be applied to the most frequently occurring mental illnesses, those which present the most potential for improvement, or a combination of the two. Psychiatric illnesses included in the first group include schizophrenia and dementia, and those with potential for improvement include anxiety and affective disorders.

In addition, a decision must be made whether to try to identify an "outlier" group of professionals whose activities deviate substantially from the norm or to try to improve the quality of care given by the average clinician (4, 27, 67). An example of the former would be a clinician who routinely prescribes excessive amounts of minor tranquilizers to most patients. The latter is represented by the performance of clinicians in evaluating and managing identified physical problems of psychiatric inpatients (68).

The determination of what to monitor is a two-step process. First, a clinical problem is identified; then the specific indicator and method of measurement are determined. Psychiatric problems or aspects of care can be broadly divided into three referent categories: condition, diagnosis, and treatment. The first category includes psychiatric symptoms or behaviors that by themselves are not sufficient to allow a diagnosis but are important with regard to the patient's adaptation and interaction with the world. They include symptoms and behaviors such as violence, agitation, withdrawal, confusion, noncompliance, and physical weakness. The second category consists of problems with the correct application of the standard diagnostic system and the appropriate use of various assessment methodologies, including diagnostic interviewing, psychometric testing, and the new scanning technologies such as computerized axial tomography and nuclear magnetic resonance. The final group consists of all aspects of treatment with psychopharmacological agents and the various modes of psychotherapy and behavioral therapy.

Selecting Indicators and Setting Thresholds

The selection of salient clinical indicators for the referent categories described here can be difficult. Williamson (69) has noted that most current medical literature is irrelevant to immediate decision making in quality assurance and medical care. This opinion was reinforced by JCAHO (24), which reported that the clinical literature provided little assistance in efforts to define usable, precise indicators. JCAHO had to rely on experts to develop indicators based on their professional judgment. Williamson (70) has acknowledged this problem and suggested a structured procedure for helping clinicians determine and establish priorities for clinical indicators. Despite the difficulties, it is possible to identify indicators that have some validity in the sense of demonstrated relevance to outcome and others that appear intuitively relevant. For example, condition indicators might include assaults by patients against other patients and staff, the incidence of agitation or confusion among elderly patients, suicide gestures and attempts, binge eating, and patient falls leading to substantial injury. Examples of diagnosis indicators consist of misdiagnosed organic causes of psychiatric illness, frequent changes of diagnosis, the use of unusual or non-*DSM* psychiatric diagnoses, incorrect or poorly substantiated diagnoses, poorly documented history or mental status examinations, and incomplete medical screening (71; *DSM-III-R*).

Treatment indicators can be subdivided into those pertaining to methodology, complications, and failures of treatment. The first depends on criteria for efficacious treatment based on either outcome studies of specific therapies or expert opinions. Treatment methodologies can be pharmacological, psychotherapeutic, social, or a combination of these three. Psychopharmacological process indicators are the most easily developed because clear criteria for the successful use of these agents have been established on the basis of extensive outcome studies (31). Examples include prescription of appropriate amounts of antidepressant medication for major depression or lithium for bipolar illness and the inappropriate prescription of neuroleptic medication or benzodiazepines. Indicators can be identified for short-term, intermediate, and long-term outcome of the treatment of psychosis or affective disorder. For example, if an agitated schizophrenic patient is admitted to the hospital, the immediate or short-term outcome must be control of the agitation within minutes or hours (72). The intermediate outcome would be the stabilization of the patient for discharge and the maintenance of control of the psychosis during the immediate discharge period. Finally, the long-term outcome might be the control of the patient's psychotic symptoms for many months. Outcome indicators can also be developed for some psychotherapies, such as behavior therapy, for which quantitative measures of outcome are an intrinsic part of the therapy. Insight-oriented psychotherapies are considerably more difficult to quantify, especially when the goal of therapy is structural change in the patient's personality (73). However, some scales have been developed to measure personality change, especially in brief psychotherapy (74, 75). Given its complex multivariate nature, it may be too early to create valid and reliable indicators for long-term insight-oriented therapy (76).

The most frequent treatment complication indicators are related to the use of pharmacological agents. Common examples are medication side effects such as dyskinesias produced by neuroleptics, confusion in the elderly produced by anxiolytics, serious drug-drug interactions or drug reactions, and medication noncompliance. Indicators for nonpharmacological therapy could include long-term memory loss or myocardial infarction following ECT. Other indicators may measure complications of the psychosocial component of treatment, such as patient disruption within a group therapy setting or the development of a pathological transference. Finally, examples of treatment failures include discharge of a patient against medical advice, failure to resolve any portion of the main psychiatric problem, and suicide.

Once an indicator is identified, a threshold level must be established. Some indicators such as suicide or unexpected death should have a threshold of 100% so that all instances are reviewed. Sometimes the clinical literature can be helpful in setting a threshold. Michel and Kolakowska (64) surveyed the prescription patterns in two psychiatric hospitals and found that 37% of patients were receiving two or more psychotropic drugs at the same time. These data can be used as a guideline in setting a threshold. For example, the threshold could be set at 37% or, if this is felt to be excessively high, at 25% or 30%. When there are no empirical data to guide clinicians in setting a threshold level they must rely on their clinical experience and intuition. Once set, the threshold may be revised as data are collected and the prevailing level of care determined.

The Data Source and Covariate Risk Factors

Finding a reliable and valid data source for quality assurance monitoring presents another problem. Most clinical data are abstracted from medical records. This assumes that there is a direct correlation between the completeness of the medical record and the quality of care. However, there are conflicting studies in this area and some concern that the incompleteness of the medical record may present problems for either process or outcome quality assurance monitoring (40). Fessel and Van Brunt (77) found little correlation between the quality of care for appendicitis or myocardial infarction and the quantity or quality of recorded data in the chart. Lyons and Payne (78), on the other hand, concluded in their study that the quality of medical records and medical care were directly correlated. Donabedian (28) has stated that the failure to record negative findings and the paucity of information on what the patient was told produce important gaps in the medical record. He suggested that the medical record may have to be altered to make it more suitable for quality assurance. Given these problems with the medical record, it is often useful to use a separate evaluation instrument to collect data. For example, a short mental status questionnaire could be used to screen for an organic mental disorder (71), a depression inventory could be used to screen for mood disorders (79), and the Brief Psychiatric Rating Scale (BPRS) (80) or the SCL-90 (81) could be used to monitor general symptoms.

Once the data source has been determined, the risk or severity factors that produce variability in the diagnostic or treatment process must be identified. For example, risk factors for the misdiagnosis of organic psychiatric disorders might include the patient's age and concomitant medical or psychiatric illnesses and those for violence could include a previous criminal record of violence. Covariate factors for the successful treatment of psychosis with neuroleptic medication might be the severity of symptoms, the number of previous psychotic episodes, and a positive response to the medication in the past.

Problems Implementing Quality Assurance Monitoring

There are several barriers to the implementation of quality assurance programs. Authors have commented on the general resistance to change within many institutions and the resentment felt by professionals due to incursions by the government and other regulatory agencies demanding accountability (48, 82–84). Some institutions have attempted to link quality assurance activities with continuing medical education under the assumption that deficiencies are due to a lack of knowledge rather than to ingrained patterns of practice (85). However, education alone is often not sufficient to change the habits of practitioners, and fiscal or administrative pressure must be applied (15, 35, 86). Another common early difficulty is the identification of too many indicators that vary in their importance. Therefore, it is important that the indicators be assigned priorities, since monitoring a few important indicators is more important than monitoring many trivial ones (87). Finally, far more energy is often invested in monitoring than in subsequent efforts to rectify identified problems in the provision of care. In response to these problems, JCAHO has repeatedly emphasized that the ultimate goal of all quality assurance monitoring is the resolution of problems that have been identified, not the collection of data.

CONCLUSIONS

Quality is in the eye of the beholder. What the physician considers a substantial achievement the patient may consider less so. Much of what we do can be described as grappling with the limitations of our capacity to reduce an onslaught of data into meaningful patterns that we can use to guide our treatment decisions. The increasing discontent of patients and society may partially be related to our reluctance to communicate directly to them the uncertainties of medicine and the variable if not capricious definition of quality. In a society where a major automobile company proclaims that "quality is job one" and a small town doughnut shop advertises that "quality isn't our goal, it's our standard," the precise meaning of quality is obscured. The word is used everywhere, and the consumer or patient expects nothing less even if he or she is not sure what quality is. Unfortunately, patients often equate quality care with complete success. This unrealistic assumption is a product of a consumer society but also partially the fault of the medical profession, which has led patients to have such high expectations. Education about the realities of medical care, not more quality assurance monitoring, is the only remedy for this problem. What quality assurance monitoring can provide is some uniformity of medical care and some assurance that care is being provided according to agreed-on standards even if those standards are still imperfect.

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Comorbidity of Substance Abuse and Other Psychiatric Disorders in Adolescents

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Psychopathology coexisting with substance abuse in adolescents is often encountered in a variety of clinical settings. Research findings suggest a major role for substance use in the etiology and prognosis of psychiatric disorders such as affective disorders, conduct disorder and antisocial personality disorder, attention-deficit hyperactivity disorder, and anxiety disorders. Psychiatric disorders also appear to have an important role in the etiology of and vulnerability to substance use problems in adolescents. Although the comorbidity of substance abuse and other psychiatric disorders in adolescents is recognized as an important factor in the treatment of adolescents, further research is needed to establish its prevalence, genetics, and clinical implications.

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As both the government and the media focus their attention on the problems of substance use and abuse among adolescents, clinicians and investigators have renewed their efforts to understand, treat, and prevent youthful involvement with drugs and alcohol. According to a press release issued by Johnston et al. through the University of Michigan News and Information Service in 1988, an annual survey in 1987 reported that 57% of high school seniors in the United States had tried an illicit drug. Ninety-two percent of those surveyed had used alcohol at some point in their lifetime, 5% reported daily drinking, and nearly 40% reported having at least one occasion of heavy drinking in the past 2 weeks.

Adolescent substance users have a greater vulnerability to accidents, injuries, and a variety of dangerous behaviors. Alcohol-related motor vehicle accidents are the leading cause of death among U.S. young people 15–24 years old, and elevated alcohol levels are often found in victims of suicide and homicide (1). It is not surprising, therefore, that a consensus opinion views substance use and abuse among adolescents as a major public health problem. The development of effective prevention and treatment of substance abuse among adolescents demands elucidation of risk factors for these disorders. Despite efforts to consider substance abusers as a unitary, homogeneous group (2), some studies have dispelled such a notion and suggested that alcoholics, for instance, can be classified into subgroups on the basis of similar etiology, family history, course, prognosis, and treatment response (3). Reduction of the diagnostic homogeneity among patients classified as having substance abuse disorders offers potential benefits for improved diagnosis of and treatment selection for subtypes of substance abuse disorders.

Comorbidity of substance abuse with other psychopathology forms the basis for a classification system to diagnose patients who are similar not only in terms of presenting phenomenology but also in their course and response to standard treatments. The study of such comorbidity among adolescents might point to specific factors in the development of substance abuse disorders in both adolescence and later adulthood and lead to more specific and effective treatments for substance abuse in youth.

In this review we will discuss the comorbidity of substance abuse and other psychopathology among adolescents in terms of 1) methodological problems encountered in research into comorbidity, 2) comorbidity of substance abuse and specific psychiatric disorders and evidence in the literature supporting possible comorbid relationships and the relevance of such comorbidity to adolescents, 3) specific questions about adolescent comorbidity suggesting specific research directions, and 4) the relevance of comorbidity in the clinical evaluation of adolescents with substance abuse problems and psychiatric symptoms.

METHODOLOGICAL PROBLEMS

One of the primary obstacles blocking research into the comorbidity of substance abuse and other psychiatric disorders is the lack of valid, reliable criteria for the diagnosis of substance abuse. *DSM-III* and *DSM-*

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III-R propose categorical definitions of substance use diagnoses that rely primarily on criteria of pathological use. These pathological or maladaptive patterns of substance use are specified in the criteria in terms of impairment in social functioning and negative social or psychological consequences of substance use. The revised criteria for substance use disorders in *DSM-III-R* correspond to features of a dependence syndrome (4) and place more emphasis on a variety of substance-seeking and substance-taking behaviors than on the presence of tolerance or withdrawal symptoms.

Applying either the *DSM-III* or the *DSM-III-R* criteria to the classification of substance use or abuse in adolescents presents problems. The inclusion of criteria for impairment in social functioning assumes that negative social consequences are the result of the substance abuse and not due to preexisting factors, including another psychiatric disorder or the coexistence of substance use and other psychopathology. Substance use by adolescents is almost always illicit, and certain negative consequences follow from this proscription rather than necessarily from the properties of the substance being used or from the behavior of the substance user. Any definition of adolescent substance abuse or dependence that uses negative consequences or functional impairment as criteria for diagnosis will produce similar difficulties because it is extremely hard to disentangle the relative contributions of substance abuse and a general pattern of adolescent deviant behavior to "functional impairment." A similar argument can be made for confusing deviant behavior with the more specific label of substance abuse in adults as well. Moreover, as with many other *DSM-III* or *DSM-III-R* diagnostic categories, no studies confirming the reliability or validity of the criteria exist.

An alternative to categorical classification is the dimensional approach. The dimensional assessment of substance abuse uses quantitative measures as a basis for defining abuse and avoids setting arbitrary levels of use to establish a classification system for substance use and abuse. Although these models assume a unimodal, continuous distribution of use within the population, this does not obviate the need for cutoffs on dimensional scales that have discriminative and predictive utility.

The definition of psychopathology coexistent with substance abuse presents a host of problems. Differences in the rates of such comorbidity obtained in previous studies may be due to differences in the samples studied, the type and method of assessment, the mental status of informants, and the timing of the assessment. Psychiatric diagnoses or collections of symptoms have been determined by assigning diagnoses based on various diagnostic criteria for psychopathology from data obtained by using methods ranging from self-rating scales completed by substance abusers to clinical interviews (using either unstructured or structured formats) of substance abusers or family members. Self-reports may rely too much on the informant, whose clinical state may be labile. Keeler et al. (5) pointed to the wide range (3% to 98%) of estimates of depression in alcoholics in several studies and stated that this range resulted from the wide array of diagnostic criteria applied and from the use of dimensional, self-report instruments as a basis for symptom description or diagnosis. Structured interviews, although possibly improving the reliability and completeness in detecting psychopathology, may also be affected by informant status. These assessment factors, most closely examined among adults, are equally important in the evaluation of psychopathology in adolescents. Direct interview of the adolescent, in addition to a parent interview, provides a more valid estimate of psychopathology than an interview with a parent alone, yielding more diagnoses and information either underreported or not reported in the parent interview (6).

Timing of the assessment is also crucial. In studies using hospitalized groups of substance abusers, assessment was sometimes made soon after admission, thus perhaps confusing the appearance of psychiatric symptoms produced by direct pharmacological effects of the abused substance with symptoms truly representing a major psychiatric diagnosis. For example, despite the high incidence of depressive signs and symptoms in hospitalized alcoholics, the affective symptoms of a majority of such patients remit within 2 weeks of abstinence without further treatment (7). Psychotic symptoms, as manifested by alcoholic withdrawal, hallucinations, and/or paranoia in the presence of a clear sensorium, usually clear within days or weeks without antipsychotic treatment. Thus, use of an appropriate and consistent time frame for the assessment of symptoms in substance-abusing adolescents is necessary to determine the temporal relationship among comorbid conditions.

In studying comorbidity, how do we order the multiple coexistent diagnoses or define the principal diagnosis or problem? Possible solutions to the appropriate classification of psychopathology and its relationship to alcoholism include classification of diagnoses using a primary-secondary paradigm (8) or a hierarchical approach (9). The primary-secondary classification refers to ordering the diagnoses according to their chronological appearance: the diagnosis whose signs and symptoms appeared first is considered primary and the later-appearing diagnoses are considered secondary.

Several studies have examined the value of the primary-secondary distinction and have found that it reduces diagnostic heterogeneity by distinguishing groups in terms of differing onset, course, prognosis (10), family history, and prevalence of the coexisting psychiatric disorder (11). On the other hand, the hierarchical approach of ranking diagnoses on the basis of exclusion criteria or the perceived primary diagnosis to be studied can create problems in studying the relationship between two or more disorders. Imposing a hierarchical scheme in which probands with overlapping symptoms are excluded or multiple diagnoses are reduced to a single diagnosis can obscure important variations in the familial transmission of two coexisting disorders such as panic disorder and depression (12). Hierarchical ranking based on severity or even chronological appearance of each coexistent disorder may obscure the true relationship between the coexistent disorders and thus preclude the identification of valid subtypes based on comorbidity.

Most of the existing studies examined the occurrence of comorbidity in hospital or clinic samples and might lead one to conclude that certain patterns of comorbidity are intrinsic to the illness rather than secondary to the sampling frame. Comorbidity may be a function of severity, and thus patients with comorbid conditions may be more likely to seek or enter treatment. Such a selection bias, also known as Berkson's bias (13), would likely yield spurious associations between substance abuse and comorbid psychiatric disorders. To be generalizable, future investigations need to recruit probands from a wide range of clinical settings in addition to subjects from the general untreated population.

RELATIONSHIPS BETWEEN COEXISTING SUBSTANCE ABUSE AND PSYCHOPATHOLOGY

Relationships between substance abuse and most, if not every, psychiatric symptom and/or disorder have been hypothesized. Among the most common psychiatric disorders related, in some manner, to substance abuse are affective disorders, antisocial personality disorder, anxiety disorders, and eating disorders. In adolescents, this list expands to include conduct disorder (the childhood-adolescence prodrome of antisocial personality disorder) and attention-deficit hyperactivity disorder. Although a number of possible relationships between coexisting substance abuse and psychopathology exist, in this review we will consider these psychiatric disorders in terms of several possible relationships suggested by Meyer (14). These include 1) psychiatric symptoms or disorders developing as a consequence of substance use or abuse, 2) psychiatric disorders altering the course of substance abuse, 3) substance abuse altering the course of psychiatric disorders, 4) psychopathology, both in the individuals and their families, as a risk factor for the development of substance abuse, and 5) substance abuse and psychopathology originating from a common vulnerability. We will explore affective disorders, conduct disorder and antisocial personality disorder, attention-deficit hyperactivity disorder, anxiety disorders, eating disorders, and schizophrenia in terms of these five relationships. The literature on comorbidity in adults will be used as a departure point because the literature discussing adolescent comorbidity is much less extensive. Relevant studies of adolescent comorbidity will also be examined in an attempt to formulate the implications of this research for the further study of adolescents with coexisting disorders.

Affective Disorders

Affective disorders are perhaps the most studied psychiatric problems coexisting with substance abuse. Among the theoretical and empirical relationships between affective disorders and substance abuse are the high prevalence of coexisting affective disorders and substance abuse in cross-sectional studies, affective symptoms or disorder developing as a consequence of substance abuse, affective disorders and substance abuse altering the course of the coexistent disorder, affective disorders as a risk factor for the development of substance abuse, and affective disorders sharing a common origin or being the result of a common vulnerability. The high prevalence of depressive symptoms in adult substance abusers is well established. Various adult studies show high rates of depressive symptoms in alcoholics (6) as well as affective disorders in a community sample of alcoholics (15), among inpatient drug abusers (16), and among both outpatients and inpatients receiving treatment for cocaine abuse (17). For adolescents, several studies have identified depression among a larger list of psychosocial and personality correlates of drug use (18) or risk factors in the initiation and maintenance of drug use (19–21). However, these studies did not establish a diagnosis for depressive disorder based on operational criteria, nor did they provide measures for severity.

In a study of adolescents seen for psychiatric evaluation in a general hospital emergency room, Reichler et al. (22) found that almost half of those with elevated blood alcohol levels (17% of the total sample) had at least one additional psychiatric diagnosis and that the most common diagnosis was depression. However, this study relied on chart review and a group presumably more severely ill than the general population. Kashani et al. (23) interviewed 100 adolescent substance abusers in a drop-in counseling center for young people and found that 16% showed evidence of double depression (a major depression superimposed on a dysthymic disorder). These findings, however, might be explained by a treatment-seeking bias toward more severely ill patients.

In a study of symptom frequency and severity in depressed adolescents, Ryan et al. (24) reported that excessive use of alcohol was associated with the psychotic subtype, a suicidal plan or attempt, phobia with avoidance, and conduct problems and conduct disorder. The use of other illicit drugs was associated with the psychotic subtype of depression as well as with conduct problems and disorder.

In addition to evidence of high rates of depressive symptoms with substance abuse, there is also evidence that dysphoria occurs subsequent to acute or chronic substance use. In acute alcohol use, alcohol is often initially perceived as a stimulant with a euphoric effect. However, as the blood level drops, euphoria changes to dysphoria and irritability (25). After chronic alcohol use, the development of more persistent affective symptoms is common. Such symptoms are likely to clear within several days or weeks of abstinence alone (26), although there may be a subgroup of patients who display serious, debilitating depressive symptoms after relatively long periods of abstention (27).

Future studies focusing on epidemiologic aspects of comorbid substance abuse and affective disorders in adolescents should use strict diagnostic criteria to define the presence of each disorder in both substance abuse treatment and psychiatric treatment groups, respectively, as well as in nontreatment groups. As in studies of adult groups, research must consider the timing of the evaluation of depression relative to the duration of abstinence.

The presence of affective symptoms appears to affect the course of alcoholism and substance abuse adversely. Alcoholics with depression have been found to have become alcoholic at an earlier age and to have had a more rapid course to problem drinking than alcoholics without additional psychopathology (28). In follow-up studies of adult alcoholics and opiate addicts, coexistent psychiatric diagnoses, including depression, predicted poorer treatment outcome in male alcoholics and opiate addicts, but female alcoholics with major depression had better outcomes than those without depression (29). A better prognosis has been observed in alcoholics with primary affective disorders than in those with primary alcoholism (30), but the presence of major depression did not alter the course of alcoholism in some samples of inpatient alcoholics (31). These differences may be related to variations in socioeconomic variables, inpatient versus outpatient samples, and other differences in diagnosis and treatment criteria. Few studies have controlled for the types and amount of treatment provided. Psychiatric disorders may contribute nonspecifically to the severity and course of substance abuse by reducing treatment compliance and increasing global impairment. McLellan et al. (32), in reporting on an inpatient adult group of substance abusers, found that the severity of the comorbid psychiatric condition, regardless of the diagnosis, was the best single predictor of treatment response.

Much confusion can arise in the attempt to determine whether the substance abuse is altering the course of the psychiatric disorder or vice versa. Studies examining alcohol use in patients with bipolar disorder provide an excellent example of the difficulties involved in the attribution of primacy in substance abuse-psychopathology relationships. Increased alcohol consumption during the manic phases of bipolar patients supports the conclusion that the severity of the bipolar illness might be increased by drinking (33, 34). Akiskal et al. (35) found that substance abuse with minor mood swings progressed to full-blown bipolar disorder in 39% of the juvenile offspring or siblings of adult bipolar patients. However, it is equally possible that mania predisposed these subjects to increased substance use.

To consider depression as a risk factor for substance abuse in a nonprospective study, depressive symptoms should antedate the abuse of the substance. Specifying the chronology of symptom appearance has led to the primary-secondary diagnostic paradigm, developed originally for affective disorders and substance abuse. Taking this dichotomy one step further, Winokur (36) divided depressive disorders into two subtypes: 1) depressive spectrum disease, seen primarily in women with a family history of depression and male alcoholism, and 2) pure depressive disease, which has a later age of onset and a family history of depression only. Depression secondary to alcoholism has been reported as more similar to alcoholism than to depression in course (37). In retrospective studies, the patient's report may have questionable reliability due to the patient's labile clinical state and poor recall of past symptoms and when they first appeared (16). Adolescent substance abusers may be less cognitively impaired because of the relative brevity of their substance use and may be able to report more accurately the chronology of their substance use and the appearance of psychiatric symptoms.

In a cross-sectional study of 424 college students, Deykin et al. (38) found that alcohol abuse was associated with major depression but not with other diagnoses. Substance use was associated with both major depression and other psychiatric diagnoses. The onset of the major depression almost always preceded the alcohol or substance abuse, thus supporting the consideration of depression as a risk factor for subsequent substance abuse in adolescence or young adulthood. Although the college sample of Deykin et al. may not be representative of the general population, the results may point to a particular relationship between depression and substance use in this subgroup of adolescents. Similarly, data from the National Institute of Mental Health Catchment Area Program (39) showed evidence that respondents with early onset of a major depressive episode or anxiety disorder had a doubled risk of later drug abuse or dependence. Johnston and O'Malley (40) found that, in response to self-report questionnaires, 23% of U.S. high school seniors mentioned boredom as an explanation for their drug use. "To get away from my problems or troubles" was mentioned as a reason for drug use by 22% of this same study group. This suggests attempts at self-medication for possible depressive symptoms.

Unfortunately, as in substance-abusing adults, few longitudinal or prospective studies have examined the development of substance abuse in adolescents. The finding of Deykin et al. (38) of high rates of primary affective disorders raises the possibility that adult studies have mislabeled many substance abusers as having secondary affective disorders due to poor historical data and patients' difficulty with recall.

There is a paucity of longitudinal or prospective studies examining the patterns of depressive symptoms and the development of substance abuse in adolescents. Patterns of affective symptoms and differential treatment response should be compared longitudinally in both an adolescent study group with coexisting substance abuse and affective disorders and one with affective disorders only.

Psychopathology as a direct risk factor for the subsequent development of a substance abuse disorder in individual adolescents is only one aspect of risk. Another approach to examining the risk of comorbidity of substance abuse and affective disorders is through family-genetic studies. The existence of psychopathology in the families of adolescents raises the possibility of a familial or genetic risk factor for substance abuse disorder. For example, there is evidence (7, 36) that the offspring of depressed probands have a high risk of substance abuse disorders. In adult family studies (41), the families of probands with "reactive depression" or depressive spectrum disease were found to have a high risk of alcoholism and affective disorders. In family studies of bipolar patients (42), high rates of alcoholism were found in the families of bipolar patients. These findings suggest the existence of a depressive spectrum or a broader, shared genetic vulnerability to various forms of psychopathology, with the underlying genetic or familial risk manifested in different disorders such as alcoholism or affective disorders, mostly along gender lines.

Weissman et al. (43) did not find a higher rate of alcoholism among the relatives of depressed patients than among the relatives of normal control subjects, although other studies (37) support the finding that probands with alcoholism secondary to affective disorders have fewer alcoholic relatives and more depressed relatives than do primary alcoholics. Merikangas et al. (44) demonstrated the independent transmission of alcohol abuse and depression in adults. In examining familial risk factors in adolescents and children, Merikangas et al. (45) observed no higher risk of depression in children of secondary alcoholics compared with children of probands with depression only. Several other studies (10, 46, 47) also found an absence of an aggregation of alcoholism and affective disorders in families. Additional data from Merikangas et al. (48) support the idea that maternal alcoholism results in a higher risk of depression in offspring; these authors noted that maternal alcoholism was always found with depression and/or anxiety disorder and concluded that maternal alcoholism may constitute an indicator of the severity of affective disorders rather than demonstrate a transmissible vulnerability to alcoholism. Several family studies of bipolar patients (49, 50) found no higher risk of alcoholism in the families of bipolar patients than in families of control subjects.

Merikangas et al. (44) commented that the frequently observed association of affective disorders and substance abuse may be due to familial clustering of social risk factors that are related to the development of major depression, alcoholism, and other disorders. An alternative explanation is that familial depression might increase the risk of social problems or behaviors such as substance use.

Studies of risk factors need to focus on the psychiatric status and substance use patterns of the offspring of substance abusers. "Bottom-up" studies examining the psychopathology of family members of adolescents with substance use disorders and/or depression may further elucidate the relationship between substance abuse and depressive disorder. However, such family studies require large numbers of subjects and appropriate control subjects as well as complex study designs.

Conduct Disorder and Antisocial Personality Disorder

Conduct disorder and antisocial personality disorder have long been associated with substance abuse. This relationship can take several forms: 1) substance use or abuse as an antecedent to antisocial behavior, 2) antisocial behavior or substance use or abuse modifying the course of the coexistent disorder, and 3) substance abuse as a risk factor in the development of conduct disorder and antisocial personality disorder. Antisocial personality disorder frequently occurs among alcoholics (51). However, this association may be due, in part, to the fact that substance abuse is one of the diagnostic criteria for antisocial personality disorder. Additionally, intoxication with various substances leads to behavioral disinhibition, thus lowering the threshold for antisocial behavior. Associations between the use of illicit drugs and violent behavior (52) and between alcohol use and homicide (53) suggest a direct causative relationship between substance use and antisocial behaviors.

The presence of antisocial personality disorder appears to modify the course of alcoholism. Alcoholic individuals with antisocial personality disorder have an earlier onset of alcohol use and a more rapid course to alcohol-related problems than alcoholic individuals without antisocial personality disorder (54). Coexistent antisocial personality disorder also predicts poorer treatment outcome in adult alcoholics (29). Additional psychiatric disorders may further affect the outcome or response to treatment of patients with coexisting substance abuse and conduct disorder or antisocial personality disorder. Both in adult opiate addicts with diagnoses of antisocial personality disorder and depression (55) and in substance-abusing delinquent adolescent males (56), the presence of additional psychopathology was associated with greater improvement in outcome criteria in the adults and a trend toward greater improvement in the adolescents on follow-up. As noted with comorbid affective disorders and substance use and abuse, it is unclear if the contribution of antisocial personality disorder is specific or due to its effect on global functioning.

Several investigators have noted that childhood behavior problems seem to predispose to the later development of alcoholism. McCord and McCord (57) identified aggressiveness and sadistic behavior in boys as risk factors for the later development of alcoholism. Robins (58) and Kellam et al. (59), respectively, found that sociopathic behavior and aggressiveness predicted adult alcohol and drug problems. In addition, family-genetic studies suggest an heritable risk of substance abuse in families with antisocial members. Adoption studies (60) have reported a greater risk of substance abuse in individuals with conduct disorder and antisocial personality disorder.

Cloninger et al. (61) analyzed the psychiatric, criminal, and drinking histories of adopted men and hypothesized at least two distinct types of genetic susceptibility to alcohol abuse: type I, or milieu-limited, alcohol abuse and type II, or a male-limited form. The male-limited form was found to be a highly heritable one in which both male adoptees and the biological fathers had extensive treatment histories for both alcohol abuse and serious criminality. Although female adoptees in families with the male-limited form of alcohol abuse did not display excess alcohol abuse or criminality, they did show a significant excess of somatoform disorder. Cloninger et al. also found a specificity of type of inheritance: alcohol problems in the biological family predicted greater rates of alcohol abuse in the adoptee, and antisocial behavior in the biological family predicted more diagnoses of antisocial personality disorder in adoptees.

Evidence exists for an additional interactive genetic etiological relationship between antisocial behavior and drug abuse, that is, antisocial behavior in biological relatives results in antisocial behavior that in turn is associated with drug abuse (62). Moreover, Merikangas et al. (45) found that the offspring of probands with depression and secondary alcoholism had a greater risk of both alcoholism and conduct disorder or antisocial personality disorder than the offspring of probands with depression only and the offspring of normal control subjects. Although this finding suggests that alcoholism and antisocial personality disorder or conduct disorder have a shared vulnerability or a common underlying pathology, the investigators (44) raised the possibility that nongenetic factors such as family environmental instability may have contributed to the high rates of conduct disorder and antisocial personality disorder seen in this study group.

Lewis et al. (63) found a strong relationship between alcoholism and antisocial personality disorder in their study of a medically hospitalized sample, but they also reported that a family history of alcoholism depended only on the presence of alcoholism, not the presence of antisocial personality disorder, in the proband. This is consistent with the suggestion that the two disorders are etiologically independent, a conclusion supported by other studies (64, 65). Cloninger et al. (65) observed that the predispositions to alcohol abuse and petty criminality were independent of each other and that the risk of criminality in alcohol abusers was correlated with the severity of alcohol abuse but not with familial criminality. The distinction between type I and II alcohol abuse could explain the discrepant results in the adoption studies, depending on the predominance of each type in a given sample.

The association of substance abuse and conduct disorder in adolescents and antisocial personality disorder in adults appears well established. However, this may be somewhat of a tautology in view of the difficulty in separating one form of deviant behavior, substance abuse, from the larger syndrome of conduct disorder and antisocial personality disorder. Again, future longitudinal studies examining patterns of substance use and antisocial behaviors may identify subgroups of adolescents with differing outcomes and responses to various kinds of treatment.

Attention-Deficit Hyperactivity Disorder

Although several possible relationships have been hypothesized between substance abuse and attention-deficit hyperactivity disorder, which is first evident in childhood, the most studied of these relationships is that attention-deficit hyperactivity disorder is an antecedent of or a risk factor for substance abuse in either adulthood or adolescence. A number of retrospective studies (66, 67) reported a greater frequency of childhood histories of hyperactivity or minimal brain dysfunction among adult substance abusers. Such studies are limited by the lack of appropriate control or comparison groups and, more importantly, by reliance on adults' memories of childhood and adolescence. The reliability of such retrospective reports is suspect because memory and other cognitive impairments are often present in chronic alcohol abusers.

A prospective study of hyperactive children followed into adulthood (68) reported that more hyperactive subjects than control subjects had a past history of marijuana use at 10-year follow-up. At 15-year follow-up (69) there was a trend for more hyperactive subjects than control subjects to have been in the abuse category in the previous 12 months. Follow-up studies (68, 69) have found that significantly more hyperactive subjects than control subjects fell into the heavy use categories at the point of maximum use.

In a review of follow-up studies of hyperactive subjects from childhood into adolescence, however, Weiss and Hechtman (69) found that most studies did not show significantly more drug or alcohol use in adolescents who had been hyperactive than in control subjects. Blouin et al. (70) found that adolescent subjects who had been hyperactive used alcohol to a greater extent than matched control subjects with school difficulties but did not abuse alcohol any more than the control subjects. Hechtman et al. (68), in a prospective study of young adults diagnosed as hyperactive in childhood compared with control subjects, reported no significant differences in use of nonmedical drugs as well as alcohol and marijuana at 10-year follow-up. The same group of researchers (71) also found no significant evidence of greater alcohol use or abuse among the hyperactive group at 15-year follow-up. Although Gittelman et al. (72) reported that substance abuse was more prevalent in adolescents who had been diagnosed as hyperactive in childhood, all of the hyperactive subjects who later used drugs showed conduct disorder either before or coincident with the onset of substance abuse.

Several investigators have invoked family-genetic studies in an attempt to explain the possible relationship between substance abuse and attention-deficit hyperactivity disorder. Family studies (73, 74) have found high rates of alcoholism and antisocial personality disorder in the parents of hyperactive children. As these studies suggested, the relevant relationship is probably between conduct disorder or antisocial personality disorder and substance abuse and not hyperactivity. For example, Stewart et al. (75) found that childhood aggression and resistance to discipline were associated more closely with parental antisocial personality disorder and alcoholism than with parental hyperactivity. Aggressive, antisocial boys were more likely to have antisocial alcoholic fathers, whereas fathers of hyperactive probands displayed no higher rates of diagnoses of alcoholism or antisocial personality disorder. This is consistent with the findings of Tarter et al. (76), who observed no differences in hyperactivity between delinquent sons of alcoholics and delinquent sons of nonalcoholics.

Alterman and Tarter (77) reviewed the literature on hyperactivity as a risk factor for alcoholism and concluded that conduct disorder rather than hyperactivity places individuals at risk for alcoholism and that the association between hyperactivity and alcoholism is due to the observed comorbidity of hyperactivity and conduct disorder. This may be the most important criticism of the literature on substance abuse and hyperactivity. Future studies must have more selective case definition of attention-deficit hyperactivity disorder and attempt to exclude children or adolescents with conduct disorder. Studies might include nontreatment groups to minimize disruptive behavior as the common denominator between the subjects with attention-deficit hyperactivity disorder and the control subjects. Researchers might also examine whether the presence of attention-deficit hyperactivity disorder confers extra risk of future or current substance abuse in adolescents with conduct disorder.

Another relationship suggested by investigators is the use of stimulants, prescribed in the treatment of attention-deficit hyperactivity disorder, as a cause of subsequent substance abuse. Currently, there is no evidence associating long-term treatment with stimulants or other psychoactive drugs prescribed for the control of attention deficit disorder with high rates of alcohol or drug abuse in adolescence or adulthood (69).

Anxiety Disorders

Comorbidity of anxiety disorders and substance abuse and the possible role of anxiety disorders in conferring a risk of substance abuse are supported by a number of studies of adults (78–80). These studies describe high rates of anxiety disorders, including agoraphobia and other phobic disorders, among substance abusers. Many of the subjects in these studies reported the onset of anxiety symptoms before the onset of their substance abuse and related problems. Unfortunately, the focus on treatment groups in these studies leads to consideration of a bias toward both more problems and more diagnoses and also greater severity.

Forty-one percent of U.S. high school seniors responding to a self-report questionnaire about drug use (40) cited "to relax or relieve tension" as a reason for their drug use; 64% of barbiturate users, 69% of tranquilizer users, and 40% and 41% of alcohol and marijuana users, respectively, mentioned tension reduction as a reason for their drug use. Again, few studies exist that examine the comorbidity of anxiety disorders and substance abuse in adolescents, whether in treatment or nontreatment groups.

In a family study, Leckman et al. (12) reported that the relatives of depressed probands with panic disorders had a greater risk of alcoholism than the relatives of depressed probands without an anxiety disorder. Weissman et al. (9) found that the rate of substance abuse among children of probands with depression and agoraphobia was higher than it was among children of either a control group or the probands with depression only. Merikangas et al. (44) observed a greater risk of anxiety disorders in relatives of probands with alcoholism, which was specifically attributed to the presence of alcoholism plus an anxiety disorder in the proband.

There are several possible ways to link anxiety symptoms to substance abuse. Anxiety and similar symptoms are often present in alcohol, opiate, and barbiturate withdrawal syndromes (81). The possibility of a protracted withdrawal or abstinence syndrome, manifested by high levels of anxiety, should be considered. The presence of comorbidity of anxiety disorders and substance abuse is consistent with the tension reduction theory (82) and the hypothesis of self-medication (83).

Cloninger (84) proposed a subgroup of substance abusers who, according to a neurobiological learning model, seek behavioral inhibition or harm avoidance. One subtype, corresponding to Cloninger et al.'s type I alcoholism (61), is predominantly associated with women who develop psychological dependence, guilt, and depression. Closer examination of possible subgroups related to anxiety disorders or avoidant behaviors is an important goal for investigators in this area of psychiatry.

Except for the family studies described, the comorbidity of anxiety disorders and substance abuse in adolescents has not been carefully studied. The need for prospective studies of high-risk children and adolescents with anxiety symptoms or disorders is obvious. If a connection can be established between anxiety and substance abuse in youth, then primary prevention efforts or early intervention treatments may forestall the development of substance abuse in these identified high-risk groups.

Schizophrenia and Psychotic Symptoms

Drug-induced psychotic symptoms in adults have been associated with the use of hallucinogens, stimulants, phencyclidine, and cannabis (85). Sustained use of stimulants can produce a classic paranoid psychosis, and this pharmacological parallel provides a useful model for schizophrenia (84). The pattern-specific drug use behavior of schizophrenic patients may provide clues to underlying neuropathological mechanisms in the development and maintenance of schizophrenia (86).

The acute alcohol withdrawal syndromes of alcohol hallucinosis and delirium tremens can be manifested by hallucinations and psychotic agitation. Although these withdrawal syndromes are usually noted in chronic alcohol users, it is uncertain what quantity and pattern of alcohol intake are sufficient to elicit physiological symptoms in adolescents or how often withdrawal states occur in adolescents. Actual physiological dependence in adolescents appears to be rare, as noted by Vingelis and Smart (87).

Eating Disorders

Eating disorders are another group of psychiatric disorders often associated with substance abuse. Several studies (88, 89) point to a high incidence of substance abuse among bulimic patients compared with patients with restrictive anorexia nervosa. Kaye et al. (90) suggested that the decreased tension and anxiety reported after binge eating as well as the "giddy, silly or somewhat intoxicated" mood reported on termination of binge eating and vomiting are comparable to substance abuse because tolerance can develop to the tension reduction or intoxicating effects. Bulimic behavior is then continued to maintain a dependency rather than to get high. Other studies (88, 91) reported a high prevalence of alcohol and drug abuse among first-degree relatives of bulimic subjects. The greater prevalence of substance use and abuse among bulimic patients suggests shared characteristics. The observed comorbidity of eating disorders and affective disorders may explain all or part of the comorbidity of eating disorders and substance abuse. Another alternative is that bulimia, alone or in combination with other addictions, represents an alternate expression of a shared vulnerability or genetic predisposition (92). Bulik (92) suggested that the expression of this vulnerability may be shaped by individual biological factors and environmental-social factors such as cultural restrictions on female drinking and drug use.

COMORBIDITY AND THE RISK OF SUBSTANCE ABUSE

As discussed in this paper, the adult literature provides mixed support for specific comorbid psychiatric disorders influencing the risk, onset, and course of substance abuse disorders. However, there may be a nonspecific relationship between substance abuse and comorbid psychiatric disorders, perhaps best seen as the added severity of additional symptoms or problem behaviors. The mechanisms underlying these possible specific and nonspecific relationships should be described and studied in appropriate study groups.

Two theories for understanding comorbidity and the risk of or vulnerability to substance abuse deserve mention. Tarter et al. (93) reviewed the psychological and biological characteristics associated with vulnerability to alcoholism and suggested that vulnerability could be explained in terms of empirically established temperamental traits such as strength and speed of response, quality of prevailing mood, and lability of prevailing mood. Clarification of temperamental traits may be useful for identifying characteristics that distinguish alcoholic individuals or those at risk for alcoholism with such traits from those without these traits. Temperamental traits may be the basis for a common diathesis for alcoholism and antisocial personality disorder and/or other psychiatric disorders.

In a similar fashion, Cloninger (84) proposed that clinical subgroups differing in patterns of abuse, personality traits, neurophysiological characteristics, and inheritance result from various response biases or neurogenetic adaptive mechanisms that affect individuals' adaptation to experiences, including their response to the use of substances. Cloninger et al.'s type I and type II alcoholics reflect various combinations of these adaptive mechanisms that result in substance-seeking behavior and later dependence after initial or early exposure.

Substance use as self-medication of coexistent psychiatric symptoms continues to be a hypothesis worth exploring both in the clinic and in the laboratory. On the basis of psychodynamic and other clinical findings, Khantzian (94) suggested that the specific psychotropic effects of illicit drugs, especially cocaine and heroin, interact with psychiatric disturbances and "painful affect states" to predispose to addictive disorder. The addict's choice of drug is the result of an interaction between the psychopharmacological properties of the drug and the primary feeling state experienced. However, others (95) have observed that Khantzian and the literature that he cites fail to distinguish between psychiatrically induced addictive disorders and substance-induced psychopathology.

The observations that the use of alcohol and tobacco and the use of illicit substances peak during the 18–34-year-old age span and that the highest rates for prescribed psychoactive medications peak after age 26 suggest that these use patterns have similar social and psychological functions (88). In a review of longitudinal studies of both high school and college students, Kandel et al. (96) reported that many behaviors and psychological symptoms thought to be consequent to drug use actually predated substance use. Dilsaver (97) suggested that cholinergic and aminergic neurotransmitter systems influence mood, affect, and psychomotor status. Abnormal interaction of these systems, as well as supersensitivity of muscarinic cholinergic systems, forms the basis for pathophysiology of affective disorders. Drugs of abuse and medications prescribed for affective disorders have common neurochemical effects that presumably treat the abnormality. Self-medication of psychiatric symptoms may be the common denominator in explaining the relationship among various psychiatric disorders coexisting with pathological substance use.

CLINICAL IMPLICATIONS AND RESEARCH DIRECTIONS

The study of comorbidity of substance abuse and other psychiatric disorders and the results of such research offer many potential benefits to public health officials and clinicians. Through the further identification of subtypes of accompanying risk factors, more specific identification of groups at risk could be helpful in prevention, treatment, and follow-up. Due to the implications of additional diagnoses for treatment and prognosis, evaluation of adolescents would be more thorough, whether the primary problem is identified as substance abuse or other psychopathology. Increased effort would be made in obtaining a thorough family history and chronology of symptom onset. Following such a complete evaluation and differentiation of individuals into subgroups, each subgroup would likely benefit from a specific program or set of interventions. For example, tricyclic antidepressants would be prescribed for those in whom alcohol abuse was secondary to depressive symptoms. To ensure inclusion in the appropriate subgroup, patient symptoms, behavior, and response to treatment would be continually evaluated.

As illustrated by the paucity of literature examining the comorbidity of substance abuse and other psychiatric disorders in adolescents, researchers have several salient questions to answer.

1. *Nosology of substance use disorders.* Current diagnostic systems for the classification of adolescent substance use disorders have yet to demonstrate their validity. Establishing criteria for the diagnosis of substance abuse is a necessary precursor for the study of comorbidity. Establishment of a valid nosology or classification system that considers comorbidity as a possible basis for subtypes is a prerequisite for further study in this area.

2. *Frequency of comorbidity in adolescents.* Among adolescent substance abusers, how often are coexistent psychiatric symptoms or disorders found? It is important to establish the frequency of comorbidity in nonreferred groups because of the likelihood that comorbidity increases the amount of treatment seeking.

3. *Chronology of comorbidity.* Because childhood through adolescence is a high-risk period for the initial development of both substance abuse and other psychiatric disorders, the study of the chronological development of each of these disorders is feasible only in children and adolescents. High-risk strategies are likely to yield the most information about these questions. Furthermore, studies of adolescents with comorbid substance abuse and other psychiatric disorders may shed light on our present hierarchical classification schemes, such as the primary-secondary paradigm, because the chronology of the development of existing disorders is already obscured in adults with a long history of substance abuse.

4. *The genetics of comorbidity.* Researchers should continue to examine the children of probands with substance abuse disorders (that is, children at high risk), as well as the children of probands with psychiatric disorders coexistent with substance abuse. In addition, family studies of substance-abusing adolescents are needed to further disentangle the relationships between substance abuse and coexistent disorders. Ideally, these studies should involve the direct interview of the proband, use precise and useful diagnostic criteria with reliable, valid diagnostic instruments and appropriate control groups, and use nonreferred samples.

5. *Treatment of patients with comorbid disorders.* Research is needed not only to determine the most efficacious treatment or treatments for coexistent disorders but also to aid in further delineating the relationship between the coexistent disorders. Pharmacological dissection will assist in the determination of what aspects of comorbid disorders respond to various types of treatment. Psychosocial modalities, such as psychotherapy, cognitive-behavioral approaches, and social skills training, might also be used to further identify relevant treatment factors.

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Managed Health Care and the Massachusetts Experience

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Managed health care, through prepaid health delivery systems and utilization review organizations, is perhaps the greatest trend in modern health care. The authors examine the remarkable growth of managed care and outline its clinical, economic, ethical, and practical implications. They then review examples of how organized psychiatry has been involved in managed care and describe the efforts to date of the Massachusetts Psychiatric Society in this area. Managed care is here to stay. The future climate of psychiatric practice and the care available to psychiatric patients are dependent on informed and organized activities by psychiatrists and their local and national representatives.

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Managed health care is a phenomenon that had modest beginnings in the past few decades. By the 1980s, however, managed care began to expand exponentially. Estimates are that, within the next decade, managed care (as an alternate form of health insurance, as benefit management, as service delivery, or as some combination of these) is likely to encompass most of the medically insured people in the United States.

The remarkable growth of managed care is attributed to a variety of economic and social trends (1, 2). The absolute cost of health care in the United States is a primary reason for the development of managed care as a method of cost containment. Currently, more than 11% of the gross national product is spent on health care. This is more than 550 billion dollars (3), one-third of which is paid by the federal government. The phenomenal costs of health care threaten U.S. business and government with the burden of payment and a consequent diminished capacity to compete in the world market. Remarkably, these vast sums of money, the greatest in the world, are not adequate: 37 million people in the United States are not insured, and many more are underinsured (4).

A second principal reason for the emergence of alternate delivery systems is the reported oversupply of physicians (3, 5) (although this has recently been disputed [6]) and hospital beds (3, 5). Too many providers and more than enough beds place those who are seeking and managing services at an advantage because of excess supply. What has been called a "product orientation" to health care is still another factor in the growth of managed care (7; unpublished 1988 paper by Ebert et al.). Instead of professional time as psychiatry's "product," several services are now called health care products and managed care organizations are their distributional channels.

Another critical factor in the growth of managed care is the failure of the regulation efforts of the 1970s to cut costs (8). Since health care costs are escalating and previous efforts at cost containment have failed, a marketplace orientation has emerged as a potential solution to fiscal conditions that the United States cannot afford. Business, labor, and government are assuming greater control over health care financing and delivery in order to contain what they regard as a runaway system. Managed care has become the enterprise by which medicine, industry, and government are attempting to solve the profoundly complex financial, organizational, and social questions of health care today.

There is no question, in view of these trends, that something must be done. Furthermore, there is reason

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The background for this paper is derived, in part, from the work of the Massachusetts Psychiatric Society's Task Force on Managed Care, composed of Drs. Sederer (Chairman), St. Clair, Robert Dorwart, Judith Feldman, Ron Geraty, and Steven Stelovich. The views expressed, however, represent those of the authors.

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to believe that alternate management and delivery systems may represent at least part of the solution. This is a time of opportunity and a time of threat, a time for potential creativity or a time for siege and blame. The real confines of a managed accountability system can yield data and demand clinical problem solving that have heretofore been neglected. Simultaneously, genuine concern exists that, unless carefully monitored, the financial pressures of managed care will eventually translate into inadequate patient benefits, poor quality of care, and the transfer of liability for these shortcomings to the already burdened backs of psychiatrists. In response to these concerns, the Executive Committee of the Massachusetts Psychiatric Society established a Task Force on Managed Care. This paper derives in part from the work of that task force.

A full review of the subject of managed care cannot be presented here; the reader is referred to a developing literature on this subject (9–37). In this paper we will first outline the clinical, economic, ethical, and practical implications of managed care. We will then offer examples of how organized psychiatry has been and can be involved in managed care. Finally, the efforts to date of the Massachusetts Psychiatric Society will be described. Managed care is here to stay. The future climate of our psychiatric practices and the care available to our patients is dependent on informed and active professionals and consumers.

PSYCHIATRY AND MANAGED CARE

At present, psychiatrists are not nearly so involved in service delivery through managed care organizations as are our colleagues in other medical specialties. A 1986 study (29) found that 48% of office-based nonpsychiatric physicians were providing care for subscribers of a managed system, either in a health maintenance organization (HMO) setting or as a member of a group that contracted with such a system. The psychiatrists surveyed indicated that only about 2% of their income derived directly from managed systems (29), and only 3.6% (900 of 25,000) of office-based psychiatrists identified a managed care plan as their primary practice setting (29, 38, 39; March 7, 1988, memo from APA's Division of Government Relations). However, estimates based on the growth to date (28, 40) indicate that 25%–50% of the population of the United States could be enrolled in some form of managed care within the next 5–10 years. Furthermore, because these organizations contract out for mental health services, there is evidence (38) that a more accurate figure for the amount of psychiatrists' incomes coming from managed systems may be 9% rather than 2%.

The increasing role that managed care is playing in the area of utilization review is difficult to quantify. Suffice it to say that almost every major insurer (including commercial carriers, Blue Cross, Medicare, and Medicaid) has adopted or is in the process of considering some form of utilization review or case management system for hospitalized patients, done either by the carrier or contracted out to a utilization review company. In 1985, managed care systems began enrolling Medicare patients, and by 1988 there were more than one million Medicare patients covered (41). According to a March 7, 1988, memo from APA's Division of Government Relations, Medicaid patients are already enrolled in managed care in 26 states, five of which have required pilot projects. If managed care (as service delivery or as utilization review systems) has not become a regular part of the psychiatrist's practice yet, it is apt to become so in the near future.

The implications of managed care cast a long shadow. What care will we be able to provide? To whom? For how long? At what payment? With what conflicts regarding quality of care, access to care, and physician ethics? These questions are vast and crucial. They represent the basic foundations of clinical practice. They are the central questions we must ask in assessing and influencing managed care organizations and their development (42–44). The competitive marketplace of the 1980s that has enabled managed care to flourish cannot be a singular solution to the problems of providing health care to the citizens of the United States. Competition, through cost containment, can make for cheaper care but not necessarily for better care and certainly not for the equitable distribution of care. Matters of cost and efficiency, at the heart of the managed care ideology, must be balanced with considerations of quality, equality, and availability.

Physicians have found that their fiduciary relationship (founded in trust and confidence) with patients has been increasingly eclipsed by a contractual relationship with corporations in which specified, measurable services are offered at negotiated prices (45). With this, physicians are losing autonomous power over clinical practice to large-scale buyers, regulators, and consumers (46–55). Yet, it is unrealistic to expect that the open-ended cost reimbursement system can continue. Paying each provider for whatever services are rendered only encourages maximal services and inflationary costs (56). Solutions, like those of prepaid care, are attractive alternatives if financial goals (which are desirable to the patient-consumer as well as to the policy buyer) are counterbalanced by realizable clinical goals.

Although managed care may help to cap costs, it tends to separate out groups of subscribers, frequently on the basis of their being at a lower risk for illness and therefore costing less. By attracting a pool of subscribers who are at lower risk, managed care systems omit high-risk, high-cost patients, thereby transferring these patients to separate systems of care, which then absorb greater costs. There is perhaps no clearer example of this than in the care of the chronically mentally ill. For these patients the persistence and severity of their illness requires long-term care that has acute, maintenance, and rehabilitation components. Quality care for this population entails psychiatric, psychological, medical, and social welfare services, all of which are costly. Babigian and Reed (24) and Schlesinger (57) have demonstrated that this population can be covered by a capitated system if the financial compensation is adequate. In general, however, the chronically mentally ill are separated out from managed systems. Such a separation may be a business necessity, but it does not lead to equity of medical care. Separate, history has shown us, is not equal. Physicians who join and represent managed care organizations soon face this complicated ethical and social dilemma, unless the patients with chronic illness are appropriately budgeted for within the managed system.

Physicians who are engaged in the managed delivery of services also face additional ethical problems. Physicians are asked to place themselves between their patients and the "company" through their activities as gatekeepers, as utilization reviewers, and as financial partners through risk sharing (8, 58–60). Psychiatrists are spared, for the most part, a role as gatekeeper in HMOs; this job tends to fall to the primary care physician. However, if psychiatrists are involved in establishing the rules by which the gate operates (e.g., what conditions should be referred to a psychiatrist), they might face conflicts between clinically optimal treatment and potentially excessive utilization and cost (from the perspective of financial actuaries). Whether depression can be treated by the primary care physician or should be referred to the mental health section exemplifies this problem for substantial numbers of patients (61).

As utilization reviewers, psychiatrists are asked to decide whether care is needed at all, at what level (e.g., inpatient or outpatient), and for how long. Psychiatrists who represent or are financially dependent primarily on the managed system are at risk to become agents of their employer, who no longer is the patient. If, however, the aims of the physician's employer are concordant with delivery of quality care within a reasonable budget, opportunities for creative and improved service delivery can occur (62). We can see this today as managed care incentives have encouraged the rebirth of psychiatric day care programs and the advent of outpatient detoxification and substance abuse rehabilitation.

Conflicts of interest are inherent to all human endeavors and are amply represented in the history of medicine. The problems of managed care create specific incentives, namely those of doing less. Herein lie both the danger and the opportunity of managed care. We might be relieved of this conflict if consumers of health care were truly informed and acted in an informed manner (57, 63). However, this does not typify the average consumer-subscriber-patient or even many of the above-average consumers. Instead, patients generally discover the limits of their policy or benefit plan only when their health needs place them in a position to want to exceed those limitations.

PRECEDENTS FOR ORGANIZED PSYCHIATRY'S ROLE IN MANAGED CARE

The need for organized psychiatry to offer systems to examine and, when necessary, to counterbalance the powerful economic forces at work (thereby protecting itself and its patients) has already become clear at both local and national levels. The following summary of the activities of psychiatrists in Philadelphia and New Haven and at APA is meant to be illustrative, not exhaustive.

The Philadelphia Psychiatric Alliance. The principals involved in the development of this organization were Drs. Paul Fink and Peter Whybrow and attorney Mitchell Goldman. The Philadelphia Psychiatric Alliance came about in response to Blue Cross and Blue Shield's establishing a preferred provider organization with poor psychiatric benefits and fees. The district branch (Psychiatric Physicians of Pennsylvania, Philadelphia Chapter) chose to create the Philadelphia Psychiatric Alliance as a separate organization because of concerns about restraint of trade. A $50 enrollment fee was asked of 500 psychiatrists, some of whom were members of the district branch and some of whom were not (the current membership is about 600). This money was then used to create the alliance, to establish a board, and to hire leaders and staff.

The Philadelphia Psychiatric Alliance identified problematic managed care systems, first by word of mouth, then by publication (a newsletter). It has been active in discouraging hospitals and psychiatrists from contracting with what it believes to be problematic insurers. The Philadelphia Psychiatric Alliance has expanded its activities to include representing psychiatric providers of service in their contract negotiations and acting as a negotiating agency on behalf of psychiatry with insurers that are developing benefit packages. It has had success recently in bargaining with Blue Cross and Blue Shield for an enhanced and clinically flexible benefit package.

The Physician Association of New Haven County. This association was formed and funded by the Connecticut Medical Society in an unusual moment in its history, that is, when the president of the society was a psychiatrist. The Physician Association of New Haven County was established as separate from the medical society for the purpose of analyzing managed care contracts for prospective physician providers. Dr. Boris Rifkin was its first president. Unlike the Philadelphia Psychiatric Alliance, the Physician Association of New Haven County does not negotiate contracts. The Connecticut Medical Society adds $100/year to the dues of its membership to pay for this association. A newsletter entitled "Informed Consent" is published every 1–2 months and distributed to all members of the Connecticut Medical Society. This newsletter details what is known about managed systems in the area and what it is like to contract with them.

APA. APA has established a Task Force on Professional Practice Issues in Managed Care Settings. This task force has begun developing guidelines for psychiatric practice in staff model HMOs. APA has also submitted a statement to the U.S. Department of Health and Human Services conveying concerns about the apparent omission of inpatient psychiatric services as a requirement for federal qualification of an HMO. In 1987, APA wrote the Health Care Financing Administration calling for the government to monitor marketing and advertising practices of managed systems that have federal contracts. Concerns about deceptive advertising by insurers are longstanding (64, 65) and resulted in an APA Assembly Action Paper in May 1987 on "False and Misleading Advertising in the Health Insurance Industry."

In November 1988, APA sponsored a 3-day invitational symposium entitled "Psychiatry and Managed Care Systems: A Resource Symposium." Approximately 50 psychiatrists, management consultants, business executives, government representatives, and attorneys attended. The principal subject areas covered were 1) an overview of mental health services in managed care, 2) the practitioner in the managed care system, 3) issues in practice, 4) perspectives (the HMO, business community, managing psychiatrist, psychiatrist entrepreneur, hospital, state and federal government, nongovernmental third-party payer, patient, and family), 5) quality of care, and 6) initiatives from the medical community. In addition, smaller work groups met to address matters of legislation, training, ethics, the chronically mentally ill, substance abusers, guidelines for practice, research, and other topics. A variety of specific recommendations were developed for APA to consider and then act on.

MANAGED CARE IN MASSACHUSETTS

The Task Force on Managed Care of the Massachusetts Psychiatric Society sought to learn from and collaborate with the efforts of APA noted here. We also sought to determine what activities the Massachusetts Medical Society was undertaking in this area. The Massachusetts Medical Society recently developed a member service (for additional dues) that will provide analysis of contracts for physicians considering working with managed care companies (21; personal communication from G.L. Roy). The areas that the task force considered as options for the Massachusetts Psychiatric Society were different and complementary to the activities of APA and the Massachusetts Psychiatric Society. We examined and considered potential activity in three major areas. Our aim, as previously noted, was to ensure that a substantive balance weight of clinical consideration was actively present to offset the increasingly heavy weight of a dollar-driven health care system. The deregulatory atmosphere of the marketplace seemed to call for regulatory constraints imposed by governmental (or other external) agencies (66).

1. *Certification of managed mental health plans.* If the Massachusetts Psychiatric Society could develop criteria for minimal standards of care, it could invite managed care systems of all types to apply to the society for certification. Criteria could include both criteria for quantity of care and standards for clinical practice. For example, there could be criteria that measure the actual numbers in the demographics of the provider network as well as criteria that would seek to measure actual clinical care. Demographic criteria might include number of providers per 1,000 members (and a breakdown of their disciplines and professional certification), utilization rates for inpatient and outpatient care, and number of subspecialty providers (e.g., child, substance abuse, and geriatric specialists). Clinical criteria might include outcome studies, suicide reviews, and quality assurance. No accreditation, licensure, or financial contract would exist between the Massachusetts Psychiatric Society and any managed care organization that sought certification. Instead, for a minimum administrative fee, the society would examine the service delivery system. If it met the criteria, approval would be awarded.

APA has established criteria for practice for psychiatrists who work in community mental health centers (67). If such criteria were established for HMOs, they would represent nationally applicable standards that our district branch or other district branches could use in a certification process. Further criteria, needed but not covered by APA standards, could be developed on the national level or could be the work of state or regional psychiatric task forces.

2. *Certification and monitoring of utilization review organizations.* This activity would especially apply to the utilization review companies described earlier in this paper and would entail a system of certifying and monitoring the activities of these organizations. The Massachusetts Psychiatric Society could review the criteria by which these organizations determine what services to allow, the clinical credentials and authority granted to the staff that actually does the review, the procedures for appeal of denial of benefits, and the degree of financial and professional liability such organizations create for contracting psychiatrist providers. Utilization review corporations that met the standard criteria of the society would also receive some form of certification. The Massachusetts Psychiatric Society, if engaged in this activity, would keep a central file on utilization review firms, with continuous assessment and recording of their performance, including complaints received from society members and patient subscribers.

3. *A second opinion service.* Currently, when a psychiatrist or a patient disagrees with a managed care organization there is seldom an independent channel of appeal. Appeals handled by an alternate delivery system or a utilization review company obviously can suffer from bias. A second opinion service operated by the Massachusetts Psychiatric Society would make available a list of recognized psychiatrists who could provide timely consultation in their respective areas of expertise. The fee for the consultation would be paid by the managed system or the patient. The service

could be available to mental health and medical professionals of all disciplines as well as to government agencies.

In considering each of these options for activity, we quickly realized the considerable investment of society membership time, organizational effort, and expense each and all involved. For better or worse, Massachusetts is a state in which governmental regulation of medicine has reached high levels of activity. Furthermore, the use of regulation in medicine may be necessary if the social mandate of health care is to survive in the competitive marketplace (57, 68, 69). Our district branch also knew that the insurance commissioner of the state was interested in the managed care industry (70; Dec. 1, 1987, letter from the Office of the Commissioner of Insurance, Commonwealth of Massachusetts, to the executive directors of HMOs in Massachusetts). The amount and degree of work that would be necessary for the Massachusetts Psychiatric Society independently to develop and assert regulatory functions, the fact that Massachusetts (to date) has not had great market penetration by managed care firms, and the political context in which the Massachusetts Psychiatric Society resides, as well as a liaison with the insurance commissioner's office that had been established by one of us (R.L.S.), led us to begin a working relationship with the state's Division of Insurance.

The Division of Insurance had already had its legal counsel clarify, in a letter to HMO directors (Dec. 1, 1987), the mandated mental health benefits that exist in Massachusetts. Mandated benefits are statutory law in Massachusetts and encompass both mental health and alcoholism services. The insurance division was concerned that some HMOs operating in the state may not have been in full compliance with statutory requirements. The Massachusetts Psychiatric Society (and the other mental health disciplines of psychology, social work, and nursing) were in a position to enter into a working alliance with the state to assure that HMOs were in compliance with the law. Furthermore, the state needed an outside body of experts to determine if the HMO services were clinically appropriate. The Massachusetts Psychiatric Society, in turn, could benefit from the authority and administrative capabilities of the state government.

This collection of circumstances and interests made it possible for the Division of Insurance to establish a Task Force on Mental Health Benefits in Health Maintenance Organizations. Two members of the Massachusetts Psychiatric Society were asked to participate in the work of that task force. The office of the insurance commissioner also noted that the state regulations for HMOs were established well before the managed care boom and therefore should be examined to determine if they were satisfactory, especially in the areas of access to and adequacy of service. Furthermore, the commissioner's office indicated that a clinical opinion might be sought regarding the workings of the utilization review organizations, including the criteria by which clinical decisions are made and the contract requirements incumbent on participating clinicians. Finally, the commissioner's office noted that if reporting requirements of utilization in alternate delivery systems were established (e.g., the utilization of inpatient and outpatient services per member per month), the state could then monitor and compare the activity of the managed care plans operating in its jurisdiction.

The goals of the Division of Insurance were in remarkable concordance with the possible options for action identified by the Massachusetts Psychiatric Society and its Task Force on Managed Care. Consequently, we agreed to participate. In doing so, we would have to enter into partnership with a government regulation agency and with other mental health disciplines, each liaison having its own difficult and conflicted history. Not to join, however, would be to forgo an opportunity to influence managed care practice in a way we had already identified as vital. It would also splinter the strength that could exist in a confederation between government and all mental health providers. The task force began its work in late 1988. Among the initial agenda items were identifying "barriers to patient care," surveying professional and lay groups to specifically demonstrate areas of clinical practice problems, and studying and revising existing HMO regulations.

At the time of this writing, a work group has been created to develop a set of screening criteria that the Division of Insurance could apply to the workings of managed care systems in order to identify, for in-depth review, those organizations whose operations demonstrate substantially different patterns of operation.

CONCLUSIONS

Cost and efficiency, values central to a competitive deregulated marketplace, have gained unprecedented influence in the health care industry. Managed care is symbolic of that influence. Health care is fundamentally different from conventional services in a society, however. It is one thing to wait in line in a department store, another to wait in line in a hospital. It is one thing to be unable to afford cosmetics, another to be unable to buy pharmaceuticals. Cost control must be balanced against quality of care and access to care. Professional providers, consumers, and government regulators must see that health policy and practice do not escape a tradition of social responsibility. Unless psychiatrists work at the local, state, and national level to ensure available, equitable, and able medical care for our patients, we are at risk of violating the moral mandate of justice for all.

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Cyclothymic Mood Swings in the Course of Affective Disorders and Schizophrenia

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The authors assessed cyclothymic mood swings and psychosocial adjustment in 38 unipolar depressed, 27 bipolar, 35 schizophrenic, and 27 other psychiatric patients 4 years after hospital discharge and in 153 normal control subjects. The patients were significantly more cyclothymic at follow-up than the control subjects, but there were no differences in cyclothymia between the diagnostic groups. Cyclothymic patients showed significantly poorer posthospital functioning than non-cyclothymic patients. These findings raise questions concerning the scope of the hypothesized cyclothymic-bipolar spectrum. Minor mood swings in a variety of patients with poor posthospital adjustment may reflect persistent vulnerability to psychopathology.

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During the 1970s and 1980s there has been a renewal of interest in subclinical or subsyndromal forms of mood disturbance and their relationship to the major affective disorders (1–6). Both family studies (1, 3–5, 7) and psychopharmacologic studies (1–4, 8) have suggested a model of bipolar affective disorder in which the manic-depressive syndrome is at one extreme of a continuum that includes milder forms of bipolar affective disturbance. The term "cyclothymia," which refers to the phenomenon of cyclic changes in mood, was originally used by Kahlbaum (9) to refer to the entire range of bipolar affective disorders. Subsequently, the term has been applied to subclinical mood disturbances associated with specific temperamental predispositions (10) and personality types (11, 12). The extent of the hypothesized cyclothymic-bipolar continuum has long been a subject of speculation and research and remains an unsolved problem. The present research addressed this issue by assessing subclinical cyclothymic mood swings in patients with bipolar and other psychiatric disorders, as well as the relationship of these mood swings to overall adjustment at follow-up.

Exactly what constitutes clinically significant cyclothymia is unclear, and various criteria have been proposed. Currently, the major diagnostic systems in American psychiatry use the cyclothymic category for patients who persistently exhibit some symptoms characteristic of the manic and depressive syndromes without meeting either set of criteria for a full major affective episode. The Research Diagnostic Criteria (RDC) conceptualize cyclothymia as a personality disorder, while the *DSM-III* and *DSM-III-R* categorizations integrate the newer biological evidence linking some forms of subclinical mood variability to bipolar affective disorder (13). Akiskal et al. (1, 3, 4), whose research shaped these nosologic developments, studied cyclothymic patients who manifested syndromes that included mood swings and unequivocal behavioral signs. Fieve and Dunner (14) suggested "bipolar other" as a designation for patients with bipolar mood disorder who had received outpatient but not inpatient treatment. They further suggested that their "bipolar other" group corresponded to Akiskal's "cyclothymic disorder" group and that the cyclothymic personality represents a milder form of mood disorder found in untreated cases (2). Our investigation focused on cyclothymic mood variability in a broad range of psychiatric patients with and without vegetative signs. It assessed minor mood swings in both affective and nonaffective disorders rather than the presence of an affective or subaffective syndrome.

Kraepelin (10) believed that manic-depressive patients with an underlying cyclothymic temperament had a poorer longitudinal course of illness than those without a cyclothymic temperament. Klein, Depue, et al. (15–17) found that subjects with cyclothymic characteristics developed more difficulties in psychosocial functioning than those without. Whether such impairment is explicable in terms of incipient affective disorder is unknown, but it does not appear to be com-

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pletely accounted for by the development of major affective syndromes (15). Despite studies supporting the hypothesis that cyclothymic patients are at risk for developing clinical affective disorders (4, 16), the prognostic implications of subclinical cyclothymic symptoms have not been fully elucidated in either major affective disorders or nonaffective psychiatric disorders. The study of affective symptoms in schizophrenic patients has suggested that affective symptoms are associated with a relatively good prognosis in schizophrenia (18, 19). Thus, it might be predicted that in patients with bipolar affective disorder cyclothymic symptoms would be associated with poor prognosis, whereas in schizophrenic patients cyclothymic symptoms would be associated with relatively good prognosis.

The current research assessed the prevalence of cyclothymic mood swings and their relationship to the course of illness in a diverse sample of patients followed up prospectively after hospitalization. The following research questions were posed.

1. Are cyclothymic mood swings at follow-up more prevalent in patients previously hospitalized for major psychiatric disorders than in normal subjects?
2. Are cyclothymic mood swings more prevalent in patients with major affective disorders than in patients with other psychiatric disorders?
3. Are cyclothymic mood swings more prevalent in patients with bipolar disorder than in patients with unipolar disorder?
4. Is there a relationship between cyclothymic mood swings and posthospital adjustment when patients are followed up after the acute phase? If so, is this relationship stronger in patients with bipolar affective disorder, or is it equally important in patients with other forms of major psychiatric illness?

METHOD

The patient sample consisted of 127 patients who were studied at follow-up, after the most acute phase of their illness. These patients had been hospitalized at either Michael Reese Hospital (N=75) or the Illinois State Psychiatric Institute (N=52) and were then assessed as part of the Chicago Follow-Up Study, a longitudinal research program studying the phenomenology and course of major psychiatric disorders (20–24). All of the patients were diagnosed at index hospitalization according to the RDC on the basis of information gathered from the Schedule for Affective Disorders and Schizophrenia (SADS) (25), the Schizophrenic State Inventory (20), and extensive observations while they were inpatients.

The sample included 38 patients with unipolar major depression, 27 with bipolar affective disorder, 35 with schizophrenia, and 27 with other nonpsychotic, nonaffective psychiatric disorders. The latter group included patients with the following RDC diagnoses: six with borderline personality, three with anorexia nervosa, three with panic or general anxiety, two with alcoholism, one with bulimia, one with phobic disorder, one with nonpsychotic drug abuse, and 10 with other unspecified psychiatric disorders. Among the bipolar patients, 81% (N=22) were undergoing a manic episode, 15% (N=4) had a depressive episode, and 4% (N=1) presented with mixed signs of mania and depression at index hospitalization. Patients with schizoaffective disorders were not included in these samples in order to preserve conceptual clarity.

The normal sample consisted of 153 university undergraduates who voluntarily participated in the assessment of cyclothymic symptoms. In the normal sample, 51% (N=78) of the subjects were female and the mean±SD age was 18.7±0.8 years.

In the patient sample, 50% (N=63) were female, 76% (N=97) were white, and the mean±SD education level was 13.7±2.1 years. The patients' mean±SD age at index hospitalization was 23.1±3.6 years, and 77% (N=98) were either first- or second-admission patients. The diagnostic groups did not differ significantly in age ($F=1.64$, $df=3, 123$, $p>0.15$) or education ($F=1.74$, $df=3, 123$, $p>0.15$). Since the samples showed some heterogeneity in age, this factor was analyzed to detect whether it was related to cyclothymic symptoms. The correlation of −0.07 between cyclothymic symptoms and age for the total patient sample suggested that age was not a strong factor in determining the results on cyclothymic symptoms.

For the patient sample, in-person follow-up evaluations were conducted by interviewers who were blind to the patients' diagnoses. These evaluations occurred an average of 4.0 years (range=2–6) after hospital discharge. They assessed patients' symptom status and level of psychosocial functioning during the 12 months before the in-person follow-up assessment of cyclothymic mood swings. The follow-up assessments consisted of a structured interview, a series of performance tests, and several questionnaires. Additionally, a shortened version of the SADS was used to ascertain the presence of manic and/or depressive syndromes at follow-up. The follow-up battery included detailed assessments of patients' social functioning, instrumental work performance, family adjustment, psychotic and anxiety/neurotic symptoms, and rehospitalization (20, 21).

Data on cyclothymic mood swings such as highs and lows in mood and energy level were studied rather than the full cyclothymic syndrome, which includes almost continuous mood impairment and frequent near-manic episodes. Thus, the present research studied a milder form of mood swings. Cyclothymia was assessed on a three-item scale administered to the patients routinely at follow-up and to the normal sample for the purposes of this study. These items, derived from a standardized questionnaire, have been used in other large-scale studies of psychiatric patients (26).

Responses to the three items were summed to yield a cyclothymia raw score that ranged from 0 to 3. To address issues of reliability and validity, we analyzed

TABLE 1. Cyclothymia in 127 Psychiatric Patients 4 Years After Hospital Discharge and in 153 Normal Control Subjects

Group	Cyclothymia Classification[a]				Cyclothymia Score[b]	
	Low		High			
	N	%	N	%	Mean	SD
Unipolar patients (N=38)	15	39	23	61	1.71	1.14
Bipolar patients (N=27)	8	30	19	70	1.96	1.16
Schizophrenic patients (N=35)	11	31	24	69	1.91	1.01
Other psychiatric patients (N=27)	8	30	19	70	1.96	1.09
Normal control subjects (N=153)	75	49	78	51	1.47	1.19

[a] Possible cyclothymia scores=0–3; 0 and 1=low cyclothymia, 2 and 3=high cyclothymia.
[b] Significant difference between groups on full range of cyclothymia scores: F=2.43, df=4, 275, $p<0.05$.

the scale's internal consistency and its agreement with another well-established cyclothymia scale, the General Behavior Inventory (16). Our cyclothymia scale exhibited adequate internal consistency; the coefficient alpha for the three items was 0.73 for the patient sample and 0.74 for the normal sample. The normal subjects were also administered the General Behavior Inventory, a well-validated self-report instrument for cyclothymia that has been used successfully in previous studies to screen for subclinical hypomanic and depressive features. The General Behavior Inventory has been used longitudinally to study general impairment in persons at risk for affective disorders, and it has been used in family studies as well (15–17). The administration of both our three-item measure and the General Behavior Inventory to the normal subjects allowed computation of the correlation coefficient for the two instruments ($r=0.46$, df=151, $p<0.001$). This relation between the two measures of cyclothymia was stronger than the relation between cyclothymic symptoms and overall outcome in the patient population.

Analysis of variance (ANOVA) was used on the raw cyclothymia scores to compare cyclothymic features of the patients in the various diagnostic and psychosocial functioning groups at follow-up and to compare the patients with the normal control subjects. In the individual diagnostic group analyses of the relation between cyclothymia and functioning, the presence of cyclothymic features on at least two of the three items constituted the criterion for inclusion in the cyclothymic group. Thus, patients with scores of 0 or 1 fitted into the low cyclothymia grouping, whereas patients with scores of 2 or 3 fitted into the high cyclothymia grouping. Chi-square values were computed for the high and low cyclothymia groups, and Yates' corrections were applied when appropriate.

Overall posthospital adjustment in the patient sample was rated on the LKP scale developed by Levenstein, Klein, and Pollack (27), which has been used in a number of previous investigations of outcome conducted in several different settings (20–24, 27). Scores on this global measure of outcome range from 1 (adequate functioning) to 8 (very poor functioning and lengthy rehospitalization). In previous research this 8-point scale has been divided into three broad outcome categories of overall functioning designated good, intermediate (i.e., difficulties in some but not all areas of functioning), and poor (20, 21, 27). This scale considers a number of areas of posthospital adjustment, including work and social functioning, life disruptions, self-support, symptoms, and rehospitalization. Analyses of medications at follow-up in relation to cyclothymia are presented in the Results section.

RESULTS

Presence of Cyclothymia

Table 1 shows the levels of cyclothymic symptoms (low and high) and the mean cyclothymia scores of the patients, by diagnostic category, and of the normal subjects. The data from this table allow us to examine the first three research questions. An overall one-way ANOVA conducted on the full range of cyclothymia scores revealed significant between-group differences in mean cyclothymia scores. Post hoc Newman-Keuls analyses showed these differences to be attributable to differences between the normal control subjects and three of the patient groups: the bipolar, schizophrenic, and other nonaffective, nonpsychotic patients ($p<0.05$). In the patient sample there were no significant differences between the cyclothymia scores of the different diagnostic groups ($F=0.37$, df=3, 123, $p>0.40$). While the percentage of normal subjects with cyclothymic symptoms was roughly equal to the percentage of normal subjects without cyclothymic symptoms, the percentage of psychiatric patients with cyclothymic symptoms was much higher than that of patients without cyclothymic symptoms; two-thirds of the psychiatric patients had cyclothymic symptoms. The difference between the mean score of the combined patient group (1.87) and that of the normal group (1.47) was also statistically significant ($t=2.94$, df=278, $p<0.005$). We also assessed this relationship using nonparametric methods (Kruskall-Wallace and Mann-Whitney U tests), and the results were similar.

Medications and Cyclothymia at Follow-Up

A separate analysis was conducted to study the potential differences in cyclothymia between patients

TABLE 2. Cyclothymia in 127 Psychiatric Patients at Various Levels of Psychosocial Functioning 4 Years After Hospital Discharge

	Cyclothymia Classification[a]				Cyclothymia Score[b]	
	Low		High			
Level of Psychosocial Functioning	N	%	N	%	Mean	SD
Good (N=48)	22	46	26	54	1.58	1.13
Intermediate (N=45)	14	31	31	69	1.93	1.14
Poor (N=34)	6	18	28	82	2.21	0.88

[a] Possible cyclothymia scores=0–3; 0 and 1=low cyclothymia, 2 and 3=high cyclothymia.

[b] Significant difference between groups on full range of cyclothymia scores: $F=3.52$, df=2, 124, $p<0.05$.

who were taking psychotropic medications at follow-up and those not taking medications. At follow-up, 46% (N=59) of the 127 patients were taking psychotropic medications. This included 45% (N=17) of the 38 unipolar patients, 52% (N=14) of the 27 bipolar patients, 66% (N=23) of the 35 schizophrenic patients, and 19% (N=5) of the 27 other psychiatric patients.

The results indicated no significant differences in cyclothymia scores between medicated and unmedicated patients in the overall sample ($t=0.59$, df=125, $p>0.40$) or in any of the individual diagnostic groups (unipolar: $t=1.18$, df=36, $p>0.20$; bipolar: $t=-1.18$, df=25, $p>0.20$; schizophrenic: $t=0.93$, df=33, $p>0.30$; other: $t=-0.08$, df=25, $p>0.40$). There were no significant differences in cyclothymia scores between patients taking lithium and those not taking lithium ($t=0.38$, df=125, $p>0.40$), between patients taking antidepressants and those not taking antidepressants ($t=0.44$, df=125, $p>0.40$), or between patients taking antipsychotics and those not taking antipsychotics ($t=0.01$, df=125, $p>0.40$).

Caution is warranted in interpreting the comparisons of the medication data at follow-up because patients were not randomly assigned to treatment conditions but, rather, were treated with medications because of their clinical condition. Thus, it may have been more likely that patients with more severe psychopathology at follow-up were being treated with psychotropic medications than were the patients with fewer signs of severe illness.

Cyclothymia and Posthospital Adjustment

Table 2 presents data on the psychiatric patients grouped according to level of functioning at follow-up. The data from this table allow us to examine the fourth research question. The highest mean cyclothymia score was found among the patients with poor functioning, while the lowest mean cyclothymia score was found among those with good functioning. Patients functioning at an intermediate level had a mean cyclothymia score between the means of the other two groups. A one-way ANOVA for all three groups, conducted on the full range of cyclothymia scores, indicated that the patients with poorer functioning were significantly more cyclothymic than the patients with better functioning.

The poorly functioning patient group was compared to the remainder of the patient sample with respect to cyclothymic symptoms. More than four-fifths (82%) of the poorly functioning patients had cyclothymic symptoms (scores of 2 or higher), a proportion significantly higher than that of the remainder of the psychiatric patient sample (61%) ($\chi^2=4.96$, df=1, $p<0.05$). The same information was broken down further by individual diagnostic groups. Although in several of the diagnostic groups (bipolar, schizophrenic, and other) there appeared to be a relatively large percentage of cyclothymic patients among those with poor functioning, only among the schizophrenic patients was this finding significant (84% compared to 50% of the better functioning patients; $\chi^2=4.81$, df=1, $p<0.05$). For the bipolar patients, the larger percentage of cyclothymic patients among those with poor functioning (88%) than among those with good or equivocal functioning (63%) did not attain statistical significance; however, bipolar patients with positive scores on all three of the cyclothymia items showed significantly poorer overall functioning, as determined by the mean LKP scale score, than did those who endorsed none of the cyclothymia items ($t=2.98$, df=15, $p<0.01$).

Cyclothymia and Posthospital Adjustment Controlling for Affective Episodes

To control for shifts in mood attributable to manifest major affective illness, we conducted a separate analysis excluding the patients for whom there was evidence of a major affective syndrome during the follow-up year. Thus, the analysis included only those patients who did not meet the RDC for a manic or major depressive episode at any time during the preceding year. A subsample of 103 patients (81% of the total sample) had complete SADS data assessing the presence of an affective syndrome during the follow-up year. This subsample included 30 unipolar, 27 bipolar, 31 schizophrenic, and 15 other nonpsychotic, nonaffective patients. Of these 103 patients, 42 (41%) had experienced a major affective episode during the past year (29% a depressive episode only, 2% a manic episode only, and another 10% both a major depressive and a manic episode). Fourteen (47%) of the 30 unipolar, nine (33%) of the 27 bipolar, and five (33%) of the 15 other nonpsychotic, nonaffective patients had experienced major affective episodes during the past year. Surprisingly, 14 (45%) of the 31 schizophrenic patients had experienced a major affective episode during the past year (32% depressive only and 13% both depressive and manic). The net yield of these exclusions was a subsample of 61 patients who were free of major affective episodes during the follow-up year.

The poorly functioning group of patients without major affective episodes was compared to the remainder of the patient sample without these episodes on the prevalence of cyclothymic symptoms. The findings suggest a preponderance (79%) of cyclothymic patients in the poorly functioning group, although this relationship only approached statistical significance ($\chi^2=3.42$, df=1, $p<0.07$). The same information was broken down further by diagnostic groups. In the schizophrenic group without major affective episodes, poorly functioning patients appeared more likely to have cyclothymic symptoms (88%) than not (12%), although this difference did not reach statistical significance when Yates' correction was applied ($\chi^2=2.33$, df=1, $p<0.14$).

DISCUSSION

The finding that psychiatric patients were more cyclothymic than normal subjects suggests a relationship between cyclothymia and psychopathology in general. The occurrence of subclinical or subsyndromal cyclic affective disturbances has long been recognized. In particular, hypotheses attempting to link them to the affective syndromes of manic-depressive illness have been advanced (1, 10, 11). Our study investigated cyclothymic symptoms in patients with major psychiatric disorders, including major affective illness and schizophrenia. To this end, cyclothymic features were identified at follow-up in patients previously hospitalized for major psychiatric disorders. This approach contrasts with that of other studies which have focused on patients with diagnosed cyclothymic or subaffective disorders, as well as studies of normal individuals believed to be at risk for developing major affective syndromes (1, 15, 17).

The data indicating more cyclothymia in patients than in normal subjects were obtained at follow-up, when patients are not generally at the height of their illness. This may indicate that these symptoms also reflect vulnerability to psychopathology. However, while patients followed up for both affective and nonaffective psychiatric disorders were found to have more cyclothymic symptoms than normal control subjects, there did not appear to be significant differences in the prevalence of these milder mood swings between different diagnostic groups.

The current findings indicate that cyclothymic mood swings, considered at follow-up independent of vegetative signs, are no more common in patients with affective disorders than in patients with nonaffective psychiatric disorders. Similarly, patients with bipolar disorder do not have more cyclothymic mood swings at follow-up than patients with unipolar depression. Rather, our results suggest that cyclothymic mood swings are present during the posthospital period in patients with a variety of psychiatric disorders. Cyclothymic mood swings are also present, although less severe, in many normal persons.

The similar prevalence of cyclothymic symptoms across diagnostic groups, especially in patients with affective and nonaffective disorders, suggests that while cyclothymic symptoms are associated with psychopathology, they are not necessarily linked to any specific type of psychopathology. These results do not support the notion that bipolar disorder is an extension of cyclothymic mood swings along a simple continuum, since according to this model an excess of cyclothymic symptoms would be predicted for the bipolar group. On the other hand, the results do not preclude the existence of a cyclothymic-bipolar spectrum for certain groups of patients (1, 16, 17). The results suggest that cyclothymic mood swings may be present, and even related to the course of illness, without necessarily being linked to the mood disorders as formulated in contemporary nosology.

The present research also examined the relationship of cyclothymic symptoms to overall adjustment. The observation that patients with cyclothymic mood swings at follow-up functioned more poorly than those without them supports the conclusion that these symptoms are more common in patients with more severe psychopathology and problems in adjustment. It is surprising that this finding was obtained for the schizophrenic group as well as for the overall sample, and it runs counter to initial predictions. Schizophrenic patients with the highest prevalence of cyclothymic symptoms were the ones who were functioning most poorly. Although this association may call into question the notion that the presence of affective symptoms of any type can help to identify "good-prognosis" schizophrenic patients (18, 19), it is compatible with the suggestion that depressive symptoms may be a prodromal sign of relapse in schizophrenic patients (28).

The results of this study indicate that patients with cyclothymic mood swings have poorer overall outcomes, and this cuts across different diagnostic groups. The findings suggest the presence of cyclothymic symptoms that may be clinically important, but these symptoms do not appear to be on the same spectrum of affective illness as manic-depressive illness. Cyclothymic mood swings may reflect an affective disorder, but for most of the patients it seemed to be a disorder not closely related to the major affective disorders of the RDC, *DSM-III*, and *DSM-III-R*. Certain patients with severe cyclothymic mood swings could be manifesting aspects of a major bipolar disorder, but the weak relationship in the present sample between cyclothymic mood swings and a major bipolar disorder suggests that the linking of these two disorders would fit only a minority of the cyclothymic patients we studied.

Our findings raise at least two possibilities concerning the relationship of cyclothymic symptoms to overall functioning and course of illness: 1) cyclothymia can interfere with overall functioning, and 2) cyclothymic mood swings are a product of a broader underlying factor that also increases the probability of poor overall functioning. The latter possibility seems more likely, and we would propose that cyclothymic patients are more liable to respond poorly to stress and upset. It may be that this vulnerability, leading to increased cyclothymic mood swings, is related to a biological predisposition to respond—and, at times, to overrespond—to internal or external stimuli. Such overresponsiveness might be linked to poorer regulation of autonomic activity and perhaps even to a related predisposition to respond or overrespond to stimuli with a characteristic level of CNS activation (29).

Whether mood swings interfere with functioning or, like psychosocial functioning itself, reflect other underlying factors associated with vulnerability to illness, their presence may be of great interest to clinicians struggling to understand fluctuating mood swings during a course of treatment. For example, the presence of increasing subaffective mood swings may be useful not only for monitoring the course of major affective illness, as might be predicted by a cyclothymic-bipolar continuum model, but also for anticipating acute exacerbations in nonaffective psychoses such as schizophrenia. The current findings suggest that even in patients not thought to have clinical forms of affective illness, cyclothymic characteristics may be associated with substantial functional impairment. Cyclothymic mood swings may signal greater vulnerability to psychopathology in a wide range of patients predisposed to a variety of specific psychiatric illnesses. The disruptive effects of cyclothymic mood swings and factors associated with cyclothymia should be studied further.

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Spectral Analysis of Cyclic Symptoms in Late Luteal Phase Dysphoric Disorder

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Fifty-eight subjects self-referred for premenstrual difficulty were evaluated for late luteal phase dysphoric disorder through a spectral analysis technique applied to prospective symptom ratings. Data from the Schedule for Affective Disorders and Schizophrenia—Lifetime Version were used to group the subjects according to the absence or presence of past or present psychiatric disorders. The two psychiatric groups were compared with regard to both patterns of significant symptom change and premenstrual symptom severity. Differences between the groups are used to discuss issues regarding the reliable identification of late luteal phase dysphoric disorder and the impact of other psychiatric disorders on this syndrome.

(Am J Psychiatry 1989; 146:1155–1160)

The recently revised edition of APA's diagnostic nomenclature, *DSM-III-R*, includes criteria for late luteal phase dysphoric disorder in its research appendix. These criteria help identify a homogeneous group of women with a disorder reflecting an affective disturbance that regularly and repetitively disrupts normal psychosocial functioning, usually in the days just before menses. The criteria emphasize 1) affective symptoms such as depression, anxiety, or anger rather than physical symptoms such as breast tenderness, headaches, or water retention; 2) severe impairment of psychosocial functioning; and 3) confirmation of the diagnosis by prospective, daily ratings of symptom severity for at least two complete menstrual cycles.

In our preliminary studies that used these criteria, we examined a consecutive series of 100 women self-referred for a chief complaint of premenstrual difficulty. A thorough medical examination revealed no organic cause for the premenstrual symptoms. In clinically applying the diagnostic criteria for late luteal phase dysphoric disorder, we observed that the disorder was three times more prevalent among women with a past or present episode of a psychiatric disorder than among women without a past or current psychiatric disorder (1).

The criteria for late luteal phase dysphoric disorder do not incorporate standards for the magnitude of symptom severity associated with the premenstruum, nor are they explicit about the distinction between a mere exacerbation of symptoms of another disorder and a superimposition of a premenstrual disturbance on another psychiatric disturbance. Given our observed clinical concordance between psychiatric disorders and late luteal phase dysphoric disorder, our aim in this paper is to further explore the impact of a psychiatric disturbance on the variability and severity of premenstrual symptom exacerbation.

METHOD

Data from two consecutive 26- to 32-day menstrual cycles were available from 58 of the 100 women mentioned earlier. The sample was composed primarily of women who were in their mid-30s (mean age=36 years, range=23–45 years), had some college education (mean education=15.8 years, range=12–18 years), and lived in high-income households (mean income=$47,000, range=$7,000–$150,000). They reported a mean of 1.96 pregnancies (range=0–5); 11 women who had never been pregnant were included in the study. Forty-one women were married, eight were divorced, and nine were single.

After screening that included a medical history, complete physical with bimanual pelvic examination, CBC, and blood chemistry screen to rule out contributing physical disease, women were asked to provide informed consent for daily study. All women who gave consent remained free of all medication, including oral contraceptives, for the period of study. Each woman then completed 60 to 90 days of daily ratings for 21 symptoms typically associated with a premenstrual syndrome. These ratings were recorded on the Daily Rating Form (2). In conjunction with the daily ratings, each woman recorded a daily basal body temperature to document ovulation. During the period of symptom

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ratings, each woman underwent a semistructured interview with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (3), and psychiatric diagnoses were determined by applying the Research Diagnostic Criteria (4) to the SADS data.

The Daily Rating Form provided severity ratings of 21 symptoms. Each symptom was rated on a 6-point severity scale designed to reflect the degree to which it was experienced; the endpoints of the scale were anchored by the descriptive phrases "not at all" and "extreme." The rating format is designed to provide a rapid means of inspecting the daily course of each symptom's severity. This inspection method is adequate for developing a clinical treatment strategy. However, a more stringent method is required to identify a reliable syndrome if variations across days, symptoms, and women are to be considered concurrently.

RESULTS

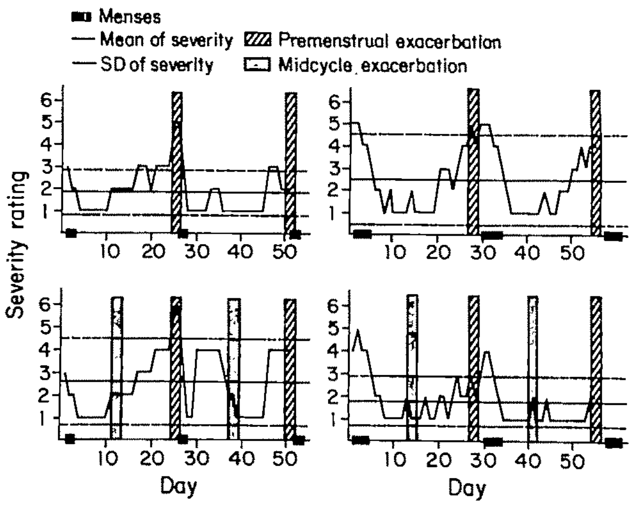
The psychiatric examination revealed that 23 of the 58 women (approximately 40% of the sample) did not meet criteria for a past or present psychiatric disorder. Of the remaining 60% of the sample (35 women), 22, or almost two-thirds, met criteria for a past episode of an anxiety or depressive disorder and 12 met criteria for these disorders during the period of the study. Two women met criteria for past substance use or abuse, and one woman met criteria for another psychiatric disorder during the period of the study.

Variability of Daily Symptom Ratings and Menstrual Cycle Effects

We obtained between 60 and 90 days of ratings of each of the 21 symptoms from each woman. We chose a spectral density analysis (5, 6) to assess the statistical significance of changes in these ratings associated with menstrual cycle phase. We applied the technique to each symptom of every woman to determine whether significant changes in symptom severity were reliably repeated from menstrual cycle to menstrual cycle. The spectral density technique determines whether the magnitude of change in daily symptom ratings for a given time interval is larger than that expected from the background variability in daily symptom ratings not associated with any time interval.

Figure 1 illustrates the approach and gives the daily ratings of four symptoms recorded on the Daily Rating Form. It is apparent in figure 1 that there was appreciable intracycle and intercycle variability for each of the four symptoms and, in addition, appreciable intersymptom variability. The spectral density analysis of the entire daily symptom record of the two complete menstrual cycles determines if there is a significant amount of symptom exacerbation regularly associated with the premenstruum or any other fractional interval of the total daily symptom record.

FIGURE 1. Spectral Density Analysis of Daily Ratings of Four Symptoms During Two Menstrual Cycles for 58 Women With Premenstrual Difficulty[a]



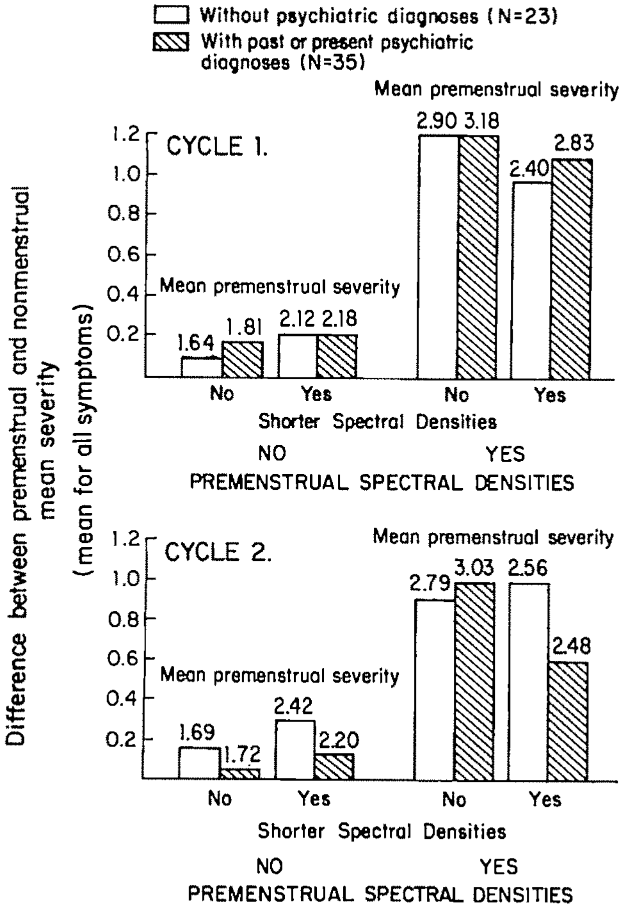
[a]Significant relationship between each symptom and the premenstruum and between the lower two symptoms and the middle of each cycle ($p<0.05$, chi-square analysis).

Each of the four symptoms in figure 1 had a significant exacerbation associated with the premenstruum, and the lower two symptoms had additional significant exacerbations associated with the middle of each cycle. Considering all 21 symptoms and all 58 women, approximately one-half (10.2±0.8) of the symptoms showed statistically significant changes associated with the premenstruum ($p<0.05$, chi-square analysis), and approximately one-third (7.8±0.5) showed one or more statistically significant changes associated with periods shorter than one menstrual cycle ($p<0.05$, chi-square analysis). These figures were not significantly influenced by the presence or absence of a psychiatric diagnosis ($p>0.05$, two-tailed t tests), which led us to conclude that neither past nor present episodes of psychiatric disturbance influenced the overall prevalence of symptoms varying with menstrual cycle phase.

Variability of Daily Symptom Ratings and Magnitude of Premenstrual Change

Having determined that psychiatric diagnosis did not significantly influence the number of symptoms that increased in severity during the premenstruum, we next considered whether psychiatric diagnosis exerted an overall effect on the magnitude of such changes. As a first step, we considered the joint influence of premenstrual spectral densities and shorter spectral densities on the magnitude of premenstrual change. For this analysis, we chose a measure of premenstrual change based on the difference between the average of the daily severity ratings during the 5 days before each menses and the average of the daily severity ratings during cycle days 6–10 and the 5 days straddling the

FIGURE 2. Relationship Between Premenstrual and Shorter Spectral Densities and Premenstrual Change Scores in 58 Women With Premenstrual Difficulty Who Did or Did Not Have Psychiatric Diagnoses[a]



[a]Premenstrual=5 days before menses; nonmenstrual=days 6–10 in addition to the 5 days straddling the cycle midpoint.

midpoint of each menstrual cycle. Our choice of these last two 5-day intervals was based on our finding that this 10-day period provided an accurate estimate of the overall severity of the daily ratings in each menstrual cycle, exclusive of the contribution of the premenstrual period.

Figure 2 illustrates the results of this analysis. From figure 2 it is apparent that the average change in premenstrual severity for those symptoms with a significant premenstrual spectral density was greater than that found for symptoms without a significant premenstrual spectral density. Those symptoms without a significant premenstrual spectral density showed premenstrual changes that were only 2%–15% of the average nonpremenstrual daily symptom severity, in contrast to changes of 34%–73% for symptoms with a significant premenstrual spectral density. This finding was expected and provided confirmation that the spectral density approach reliably identifies those symptoms which show a significant change during the premenstruum. It is apparent from figure 2 that the general effect of the shorter spectral densities was to attenuate the magnitude of premenstrual change. Figure 2 also illustrates that in symptom records with significant amounts of variability in daily severity ratings that were not associated with menstrual cycle phase, changes associated with the premenstruum were usually smaller in magnitude.

Also evident from figure 2 is that the shorter spectral densities were associated with a greater reduction in the amount of premenstrual change for the premenstrual spectral density symptoms of women with a psychiatric diagnosis than for women without a psychiatric diagnosis. For those symptoms with a significant premenstrual spectral density, the presence of shorter spectral densities reduced by 9% (averaged over both menstrual cycles) the magnitude of the premenstrual change score of women without a psychiatric diagnosis and reduced by 22% the magnitude of the premenstrual change score of women with a past or present episode of a psychiatric disorder. Among the women with a psychiatric diagnosis, the reduction was especially noticeable in the second menstrual cycle (36%).

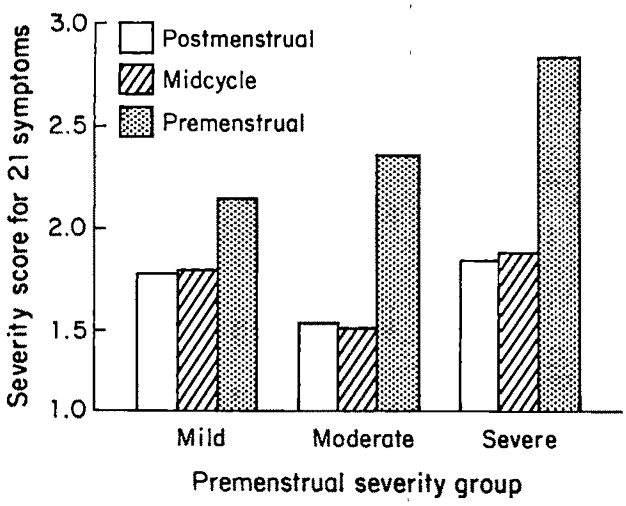
The analysis of the relationships between spectral densities and psychiatric disorders (multiple analysis of variance [MANOVA]) indicated that sizable changes could be detected in the premenstrual severity of symptoms regardless of histories of psychiatric disorder. However, because there appeared to be a significantly smaller change associated with menstrual cycle phase among women with a past or present episode of psychiatric disorder, we undertook additional analyses to explore the relationship between the severity of the premenstrual syndrome and history of psychiatric disorder.

Defining a Premenstrual Syndrome and Grading Its Severity

Our next step in the data analyses was directed at using the premenstrual spectral densities and premenstrual change data for all 21 symptoms of each woman to grade the severity of the premenstrual disturbance. In order to qualify as a positive symptom, the symptom had to have daily ratings that indicated a significant premenstrual spectral density and had to have a premenstrual change score of at least 0.5 in each of the two menstrual cycles. We chose a cutoff score of 0.5 since, as figure 2 illustrates, this score clearly distinguished between the symptoms with nonsignificant and significant premenstrual spectral densities and represented a minimum change of approximately 30% from the average severity of symptoms with significant premenstrual spectral densities during the nonpremenstrual portion of the menstrual cycle.

Using premenstrual spectral densities and the premenstrual change data, we categorized the severity of each woman's premenstrual syndrome as mild, moderate, or severe. We chose five positive symptoms as

FIGURE 3. Mean Symptom Severity Scores of 58 Women With Premenstrual Difficulty Whose Symptoms Were Mild, Moderate, or Severe



the cutoff for a moderate or severe syndrome, since criterion B of late luteal phase dysphoric disorder requires five symptoms. Women with four or fewer positive symptoms were categorized as having a mild premenstrual syndrome. Women with five or more positive symptoms were categorized as having a severe premenstrual syndrome if at least 10 symptoms showed a significant premenstrual spectral density or a premenstrual change of 0.5 or greater in at least one menstrual cycle. Women with five or more positive symptoms but with fewer than 10 symptoms showing either a positive premenstrual spectral density or a premenstrual change of 0.5 or greater in at least one menstrual cycle were categorized as having a moderate premenstrual syndrome.

This method resulted in assigning 45% (N=26) of all 58 women to the mild group; the remaining 55% were equally distributed between the moderate (N=16) and severe (N=16) groups. Figure 3 shows the mean severity scores for all 21 symptoms during the three 5-day periods of each cycle (postmenstrual, midcycle, and premenstrual) for each of these three groups. As expected, the women with severe symptoms showed larger premenstrual changes (averaged over all 21 symptoms) than did the women with moderate symptoms, who, in turn, showed larger premenstrual changes than women with mild symptoms.

When considered in the context of psychiatric diagnosis, the percent change in average premenstrual severity of all 21 symptoms across both cycles for each of the three premenstrual severity groups was 20%, 70%, and 67%, respectively, for those women without a psychiatric disorder. For those women with a past or present episode of psychiatric disorder, the percent changes for the three groups were 20%, 47%, and 45%. The larger average percent changes in the women with no psychiatric diagnoses resulted partly from their lower average severity ratings in the nonpremenstrual portions of the cycles compared to women with a past or present episode of psychiatric disorder. For the three premenstrual severity groups, the mean severity ratings for the nonpremenstrual portions of the cycles were 1.72, 1.38, and 1.66 for the women with no psychiatric disorder and 1.82, 1.60, and 1.98 for the women with a past or present episode of psychiatric disorder. For women in the moderate and severe premenstrual severity groups, the larger average percent changes in the women with no psychiatric diagnoses resulted partly from an absolutely larger change in average premenstrual symptom severity. For women without a psychiatric disorder, the average changes in premenstrual symptom severity were 0.94 and 1.12 for the women in the moderate and severe premenstrual severity groups, respectively. These figures were 0.76 and 0.88, respectively, for women in these two premenstrual severity groups with a past or present episode of a psychiatric disorder.

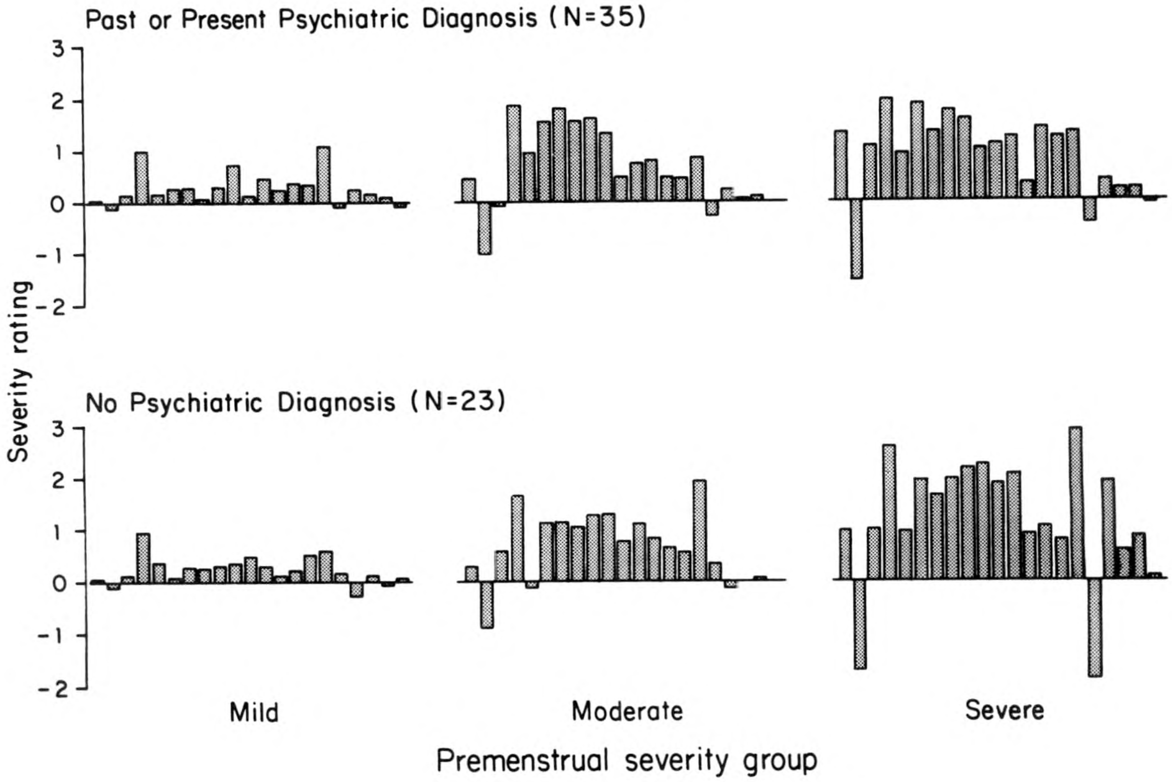
These differences suggested that the severity of a symptom during the nonpremenstrual portions of the cycle might have an influence on the premenstrual severity of the symptom that would be affected by the history of psychiatric disorders. However, in analyzing this possibility for all 21 symptoms in the aggregate, we could detect no such significant interaction ($p>0.05$, MANOVA). We therefore concluded that the simple difference between average symptom severity during the two 5-day nonpremenstrual portions of the cycle and the average severity during the 5-day premenstrual portion constituted our best estimate of the severity of premenstrual exacerbation for each symptom, regardless of the severity of the syndrome or the presence or absence of a past or present history of psychiatric disorders.

Impact of Psychiatric Diagnosis and Premenstrual Syndrome Severity on Premenstrual Change in Specific Symptoms

The last step in the analysis of these data addressed the relationships between the presence or absence of a past or present psychiatric disorder, the severity of the premenstrual syndrome, and the magnitude of premenstrual change in each of the 21 symptoms of the Daily Rating Form. This analysis was carried out to determine if any specific symptoms were relatively more sensitive to the effects of psychiatric history or syndrome severity. We considered this step important in view of *DSM-III-R*'s stipulation that "the disturbance is not merely an exacerbation of the symptoms of another disorder," especially since the definition of late luteal phase dysphoric disorder emphasizes affective symptoms and the most prevalent psychiatric disorders found in our sample and others are affective and anxiety disorders.

Figure 4 presents the premenstrual change scores for each of the 21 symptoms for each of the six groups defined by the presence or absence of a psychiatric diagnosis and mild, moderate, or severe premenstrual

FIGURE 4. Relationship Between Psychiatric Diagnosis and Symptom Severity Scores in 58 Women With Premenstrual Difficulty



syndrome. In the analysis of these data, we found that the five symptoms of enjoyment, mood swings, depression, anxiety, and irritability or anger were especially sensitive to the effect of premenstrual severity group and its interaction with psychiatric diagnosis ($p>0.05$, MANOVA). These five symptoms showed a greater than average change in the groups with severe and moderate premenstrual syndromes, and this effect was most pronounced for the women with a psychiatric diagnosis. For this group of women, the five symptoms showed an absolute average change of 81% in the severe and moderate groups, compared to changes of 35% and 47%, respectively, for the remaining 16 symptoms.

In *DSM-III-R*'s criteria for late luteal phase dysphoric disorder, at least one of the symptoms of mood swings, anger or irritability, anxiety, or depression is required in order to make the diagnosis. Our analysis demonstrates that among all women studied, these symptoms are most likely to show the largest premenstrual changes as the severity of the syndrome increases. Among women with a history of psychiatric disorders, premenstrual exacerbations in symptom severity were attenuated by greater variability and higher average symptom severity during the nonpremenstrual portions of the cycle; even so, the degree of premenstrual exacerbation of these four symptoms was significantly large and easily detectable.

DISCUSSION

DSM-III-R focuses on the need for prospective ratings in order to verify the diagnosis of late luteal phase dysphoric disorder. Except for "subjective sense of difficulty in concentrating," the items in the Daily Rating Form overlap the symptom criteria for late luteal phase dysphoric disorder. *DSM-III-R* does not stipulate criteria for either the premenstrual severity of the symptoms or the magnitude of change in symptom severity associated with the premenstrual phase of the cycle; for this reason we attempted to use the severity scores of the Daily Rating Form to develop criteria for magnitude of change that was specifically related to the premenstrual phase.

In addressing these questions, we found that among this sample of women self-referred for perceived premenstrual difficulties, an average of 10 of the 21 symptoms in the Daily Rating Form showed a significant premenstrual exacerbation. For these symptoms, severity scores averaged at least one-third greater during the premenstrual portion of the cycle. This degree of change was detectable and clearly significant for all women, regardless of their history of psychiatric disorders or the variability in their daily ratings of symptom severity. The requirement that this degree of change be present in two consecutive menstrual cycles for at least five symptoms satisfies some of the *DSM-III-R* criteria for late luteal phase dysphoric disorder;

55% of the women in our sample met this requirement. *DSM-III-R* also requires the presence of at least one of four specific symptoms (i.e., affective lability, anger, anxiety, and depression), in addition to other criteria, for the diagnosis of late luteal phase dysphoric disorder. These four symptoms were the ones that showed the largest average premenstrual change. Women with a past or present episode of a psychiatric disorder were most likely to demonstrate a significant premenstrual exacerbation as the severity of the syndrome increased.

These results support the utility of the *DSM-III-R* criteria for determining the presence or absence of a late luteal phase dysphoric disorder among women regardless of a past or present episode of another psychiatric disorder. We did not specifically address criterion D, which considers the problems of the exacerbation of another psychiatric disorder or the superimposition of late luteal phase dysphoric disorder on another psychiatric disorder; however, our results indicate that these problems could be addressed with the adoption of clearer criteria regarding the magnitude of premenstrual change and symptom severity.

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Panic Response to Lactate Administration in Alcoholic and Nonalcoholic Patients With Panic Disorder

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The authors administered lactate to 12 abstinent alcoholics with panic disorder, 10 nonalcoholic patients with panic disorder, and eight control subjects. They found that the alcoholic patients had fewer panic attacks in response to lactate infusion than the nonalcoholic patients. This finding was not attributable to differences in baseline anxiety or the change in plasma chemical values brought about by sodium lactate administration. The authors suggest that there may be subgroups of patients with panic disorder who need further characterization to meaningfully elucidate the pathophysiology of the disorder.

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Alcoholics have been reported to have a higher than expected prevalence of panic disorder than the general population (1–3). The reason for this finding is unclear. It may simply reflect the fact that patients who experience panic attacks are prone to abuse alcohol to reduce their anxiety. However, since a proportion of alcoholics develop panic disorder subsequent to the onset of alcoholism, it is possible that alcoholism, perhaps as a result of multiple withdrawals, predisposes to panic attacks. If this second postulate is correct, it is conceivable that the biochemical concomitants of panic attacks in some alcoholics may be different from those in nonalcoholic patients with panic disorder.

Sodium lactate is well established as an agent used to induce panic attacks (4). It has been shown to provoke symptoms similar to those of a panic attack in 70%–100% of subjects with panic disorder but in less than 10% of control subjects (5–7). To test the hypothesis that panic disorder in alcoholics may be different from panic disorder in nonalcoholic subjects, we administered sodium lactate to alcoholic and nonalcoholic patients with panic disorder and to control subjects. We reasoned that if the pathophysiology of panic disorder in alcoholics were different from that in nonalcoholic patients with panic disorder, the responses of the two groups of patients to lactate would also be different. To control for the possible effect of a family history of alcoholism, the group of nonalcoholic patients with panic disorder comprised subjects who were adult children of alcoholics but who did not themselves have a diagnosis of alcoholism.

METHOD

Subjects

The subjects were patients admitted to the research ward at the NIH Clinical Center. Written informed consent was provided by all patients before participating in the study. They all underwent a complete physical examination, including measures of blood chemical values and urinalysis, in addition to an independent clinical interview with a psychiatrist (D.T.G.) and a social worker who used the Schedule for Affective Disorders and Schizophrenia (SADS) (8). All alcoholic subjects fulfilled *DSM-III* criteria for alcoholism, and those designated as having panic disorder met the additional criteria for panic disorder. Subjects were excluded if they had a physical illness or a psychiatric diagnosis other than those being studied. All subjects had been free of medication and abstinent from alcohol (under daily supervision and with breath alcohol measurements) for a minimum of 3 weeks. Participants received a low-monoamine diet (9) for at least 72 hours before the lactate infusion.

The study groups were eight control subjects (five men and three women), 12 alcoholics with the additional diagnosis of panic disorder (ten men and two women), and 10 nonalcoholic patients with panic disorder (three men and seven women). The mean±SD ages for the three groups were 36.7±9.44, 34.4±7.77, and 40.1±12.08 years, respectively; there was no statistically significant difference between the groups in age according to analysis of variance (ANOVA). Five of the alcoholics with panic disorder met criteria for panic disorder before the onset of alcoholism. The se-

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TABLE 1. Baseline Measures in Alcoholic and Nonalcoholic Patients With Panic Disorder and in Control Subjects

	Patients With Panic Disorder						
	Alcoholic (N=12)		Nonalcoholic (N=10)		Control Subjects (N=8)		
Measure	Mean	SD	Mean	SD	Mean	SD	F (df=2, 27)
Psychological test scores							
Spielberger trait anxiety	49.6	7.7	46.8	9.3	27.3	5.2	21.1[a,b]
Spielberger state anxiety	42.7	15.0	47.0	10.1	27.0	8.1	6.7[c]
Hamilton depression	9.5	6.4	9.6	5.9	3.2	7.9	2.5
Analogue panic	18.7	24.8	22.0	28.4	9.3	16.3	0.6
Analogue anxiety	24.2	28.5	34.5	25.3	14.2	21.3	1.3
Analogue apprehension	25.1	29.5	38.9	18.7	13.3	18.4	2.6
Analogue muscle tension	21.6	29.3	22.4	17.8	14.1	18.7	0.3
Physiological measures							
Systolic blood pressure (mm Hg)	122.4	18.9	120.6	22.2	109.0	14.0	1.3
Diastolic blood pressure (mm Hg)	74.2	14.4	72.4	12.2	67.0	8.3	0.8
Pulse (beats per minute)	69.0	6.9	67.5	8.9	61.6	7.4	2.3
Chemical values							
Glucose (mg/dl)	100.3	9.7	96.9	16.3	93.3	9.6	0.8[a]
Sodium (meq/liter)	139.4	1.9	139.8	2.2	138.4	3.2	0.8
Chloride (meq/liter)	108.0	2.3	109.2	2.8	107.5	2.4	1.1
Calcium (meq/liter)	4.7	0.1	4.7	0.2	4.6	0.3	0.8
Phosphorus (mg/dl)	3.4	0.6	3.5	0.9	3.0	0.5	1.3
pH	7.37	0.02	7.37	0.03	7.31	0.05	8.6[b,d]
Lactate (mmol/liter)	6.9	3.8	6.9	3.7	5.6	2.8	0.4
Osmolality (mosmol/kg)	287.1	4.2	287.4	5.8	283.3	3.2	2.1[e]

[a] df=2, 26.

[b] $p<0.001$ at a Bonferroni-corrected level.

[c] $p<0.004$ at a Bonferroni-corrected level.

[d] df=2, 25.

[e] df=2, 22.

verity of the panic disorder, as judged by *DSM-III* criteria of frequency and number of symptoms during attacks, was comparable in the alcoholic and nonalcoholic patients. Seven alcoholics with panic disorder and five nonalcoholic patients with panic disorder had at least one panic attack per week in the weeks immediately before the study.

Procedure

Following overnight bed rest with nothing by mouth, an intravenous cannula was placed in the antecubital fossa and kept open with a slow intravenous infusion of 5% dextrose in water. Approximately 1 hour after the placement of the intravenous cannula the lactate infusion was started. The infusion of 0.5 M of sodium lactate dissolved in normal saline was administered at a rate of 10 ml/kg body weight for a period of 20 minutes. Blood samples for chemical analyses were obtained just before the study and immediately after the infusion was terminated. Blood pressure and heart rate were measured automatically with a Dinamap recorder (Critikon Co., Tampa, Fla.) at 5-minute intervals before the infusion and at 3-minute intervals during the study. Trait anxiety ratings on the Spielberger State-Trait Anxiety Inventory (10) were obtained at the start of the infusion. State anxiety ratings on the Spielberger inventory and 100-mm visual analogue ratings for severity of panic, anxiety, nervousness, apprehension, and muscle tension were obtained before and immediately after the infusion.

Before the study, subjects were told that the administration of sodium lactate often results in a number of somatic symptoms such as palpitations and shaking in addition to anxiety and that it might cause a panic attack. Subjects were told that if they felt the onset of a panic attack they should ask the physician in attendance to stop the infusion. The diagnosis of a panic attack secondary to lactate administration was made by using *DSM-III* criteria. Those individuals who not only reported that they were feeling out of control but also asked that the infusion be stopped were classified as having a panic attack secondary to lactate administration.

Statistics

Comparisons of baseline and change measures for the three groups were made by one-way ANOVA. The post hoc Newman-Keuls test was used to evaluate those variables which had a significant difference at the $p<0.05$ level in the ANOVA. The Fisher exact test was used to compare the number of lactate-induced panic attacks experienced by alcoholics with panic disorder with those experienced by nonalcoholic patients with panic disorder. The paired t test was used to determine differences between baseline and end measures within each of the three groups. A subsequent comparison of biochemical and psychological variables in patients

TABLE 2. Lactate-Induced Changes From Baseline to End of Infusion in Alcoholic and Nonalcoholic Patients With Panic Disorder and in Control Subjects

	Patients With Panic Disorder						
	Alcoholic (N=12)		Nonalcoholic (N=10)		Control Subjects (N=8)		F
Measure	Mean	SD	Mean	SD	Mean	SD	(df=2, 26)
Psychological test scores							
Spielberger state anxiety	20.1	14.1	16.7	9.8	15.4	12.2	0.3
Analogue panic	47.8	39.6	48.8	23.1	2.1	14.8	6.9[a]
Analogue anxiety	49.1	38.1	44.3	19.4	7.9	33.6	4.35
Analogue nervousness	46.3	28.2	43.0	16.5	19.4	39.7	1.5
Analogue apprehension	40.4	38.6	32.7	28.6	13.8	29.9	1.5
Analogue muscle tension	40.5	33.2	61.8	34.4	15.5	28.2	4.3
Physiological measures							
Systolic blood pressure (mm Hg)	10.4	7.9	18.5	17.0	17.6	14.7	1.2[b]
Diastolic blood pressure (mm Hg)	3.0	6.1	7.5	13.5	2.3	5.4	0.9[b]
Pulse (beats per minute)	29.6	13.1	34.6	14.4	37.8	6.4	1.1[b]
Chemical values							
Glucose (mg/dl)	−12.8	7.3	−10.2	14.4	−8.6	9.3	0.41
Sodium (meq/liter)	10.5	3.9	10.7	3.8	12.3	3.5	0.57[b]
Chloride (meq/liter)	−4.9	1.8	−5.6	1.8	−5.6	1.9	0.52[b]
Calcium (meq/liter)	−0.6	0.2	−0.6	0.2	−0.6	0.3	0.98[b]
Phosphorus (mg/dl)	−0.6	0.2	−0.6	0.3	−0.6	0.2	0.11[b]
pH	0.1	0.03	0.1	0.04	0.1	0.04	0.17[c]
Lactate (mmol/liter)	5.9	10.7	5.8	13.6	6.9	6.3	2.61
Osmolality (mosmol/kg)	19.9	4.3	16.6	8.5	21.0	6.3	0.95[d]

[a] $p<0.004$ at a Bonferroni-corrected level.
[b] df=2, 27.
[c] df=2, 24.
[d] df=2, 21.

with panic disorder who did or did not have a panic attack in response to lactate was made by using Student's t test. Due to insufficient homogeneity of variance, the Kruskal-Wallis analysis of variance and Mann-Whitney U test were used when necessary.

RESULTS

Two (17%) of the 12 alcoholics with panic disorder and seven (70%) of the 10 nonalcoholic patients with panic disorder experienced a panic attack as a result of the lactate infusion. Ten (83%) of the 12 alcoholics with panic disorder and three (30%) of the 10 nonalcoholic patients with panic disorder did not experience a lactate-induced panic attack. None of the control subjects had a panic attack. Significantly fewer of the alcoholic patients than of the nonalcoholic patients with panic disorder had panic attacks after lactate administration ($p=0.027$, Fisher's exact test, two-tailed). The two alcoholic patients who had a panic attack in response to lactate had the onset of their panic disorder before the onset of their alcohol abuse.

Baseline psychological, physiological, and plasma chemical values for the three groups are shown in table 1. A comparison of Spielberger trait and state anxiety scores revealed a significant difference between groups at baseline: control subjects had significantly lower anxiety ratings ($p<0.05$, Newman-Keuls). Of interest, there were no measurable differences in baseline anxiety measures between alcoholic and nonalcoholic patients with panic disorder. Similarly, blood pressure, heart rate, and plasma chemical values such as glucose, electrolytes, calcium, phosphorus, lactate, and osmolality were not different between groups. However, there was a significant difference in pH between groups: control subjects had lower values than the two patient groups ($p<0.05$, Newman-Keuls).

Table 2 shows that all groups had a rise in anxiety during lactate infusion. Visual analogue changes for panic, anxiety, and muscle tension showed significant differences between groups: control subjects showed the least change ($p<0.05$, Newman-Keuls). However, there were no differences between groups in absolute changes in either physiological measures or plasma chemical values. The systolic blood pressure was significantly higher after lactate administration than at baseline within alcoholic, nonalcoholic, and control groups, respectively ($t=4.55$, df=11, $p<0.001$; $t=3.43$, df=9, $p<0.007$; $t=3.39$, df=7, $p<0.01$), as was the heart rate within these groups ($t=7.84$, df=11, $p<0.001$; $t=7.61$, df=9, $p<0.001$; $t=16.6$, df=7, $p<0.012$, respectively). There were no significant changes in diastolic blood pressure within the groups over time.

Table 3 shows the changes between baseline and after-infusion psychological, physiological, and plasma chemistry measures in the patients with panic disorder who did or did not have a panic attack during the lactate infusion. There were no significant differences between the groups except for plasma phosphate concentration, which changed significantly less in those who panicked.

TABLE 3. Lactate-Induced Changes From Baseline to End of Infusion in Alcoholic and Nonalcoholic Patients With Panic Disorder Who Did or Did Not Have a Panic Attack During Lactate Infusion

Measure	Patients Who Panicked (N=9) Mean	SD	Patients Who Did Not Panic (N=13) Mean	SD	t (df=20)
Psychological test scores					
Spielberger state anxiety	21.6	9.7	16.4	13.6	1.00
Analogue panic	55.5	29.1	42.7	35.6	0.89[a]
Analogue anxiety	51.1	25.1	44.0	35.5	0.51[a]
Analogue apprehension	43.8	34.2	32.1	34.6	0.77[a]
Analogue muscle tension	66.6	29.1	37.6	34.6	1.97[a]
Physiological measures					
Systolic blood pressure (mm Hg)	16.7	19.3	12.2	6.9	0.79
Diastolic blood pressure (mm Hg)	10.0	13.5	1.6	5.1	2.05
Pulse (beats per minute)	33.0	17.3	31.1	11.0	0.32
Chemical values					
Glucose (mg/dl)	−9.3	15.3	−13.2	6.9	0.82[a]
Sodium (meq/liter)	9.4	2.7	11.4	4.3	−1.19
Chloride (meq/liter)	−4.7	2.4	−5.6	1.1	1.25
Calcium (meq/liter)	−0.5	0.2	−0.6	0.1	1.48
Phosphorus (mg/dl)	−0.4	0.2	−0.7	0.2	3.75[b]
pH	0.1	0.03	0.1	0.04	0.07[c]
Lactate (mmol/liter)	5.6	12.8	5.9	11.3	−0.71[a]
Osmolality (mosmol/kg)	16.0	9.0	20.0	3.9	−1.20[d]

[a] df=19.
[b] $p<0.001$ at a Bonferroni-corrected level.
[c] df=17.
[d] df=14.

DISCUSSION

In this study we found that 17% of alcoholic patients with panic disorder and 70% of nonalcoholic patients with panic disorder had panic attacks in response to lactate administration. To our knowledge, this is the first report in which a subgroup of patients with panic disorder had less of a response to lactate administration. This finding suggests that the pathophysiology of panic disorder in alcoholics may be different from that in nonalcoholic patients with panic disorder.

The cause for this finding remains unclear. If novel peripheral symptoms are important in the production of panic (11, 12), then alcoholics may be desensitized, as a result of experiencing numerous withdrawals, to the physiological effects of lactate, such as tachycardia and tremor. Second, since alcoholics tend to have elevated baseline plasma lactate concentrations (13), they may be desensitized to the physiological effects of this substance. Third, it is possible that alcoholics, as a result of changes brought about by alcohol abuse, may metabolize lactate differently. This seems unlikely, however, since plasma lactate concentrations at the end of the infusion did not differ between the groups. Finally, alcohol abuse may, in certain susceptible individuals, lead to a symptom complex similar to panic disorder but different in pathophysiology. We have postulated (unpublished observation) that alcohol withdrawal, through increases in norepinephrine and cortisol release, might kindle limbic structures to heightened states of excitability that could predispose to anxiety and panic attacks.

We have previously reported that alcoholics with panic disorder have difficulty differentiating symptoms of withdrawal from panic (14). It is important to emphasize, therefore, that all of the subjects in this study met *DSM-III* criteria for panic disorder during periods of abstinence when they were not experiencing alcohol withdrawal. In addition, our criteria for lactate-induced panic were strict. The diagnosis of a panic attack required both peripheral symptoms (palpitations, dyspnea, trembling, etc.) and a mental component characterized as loss of control resulting in the request that the infusion be terminated.

Of interest, both alcoholic and nonalcoholic patients with panic disorder had similar levels of baseline anxiety. This argues against the suggestion of Margraf et al. (15) that lactate-induced panic occurs because patients with panic disorder start the procedure with higher levels of anxiety than do control subjects. The baseline chemical values among our three groups were remarkably similar except for a lower pH value in control subjects. This difference probably has little clinical significance, but it may reflect a relative state of hyperventilation in patients with panic disorder. Lactate-induced chemical changes were also very similar among groups; only plasma phosphorus showed less of a decrease in patients who panicked than in those who did not. This is most easily explained by the fact that the infusion was stopped early in patients having a panic attack, resulting in less hemodilution. There was no difference between groups in the baseline phosphorus levels, and the greater decrease in phosphorus in patients who did not panic is at variance with the findings of Gorman et al. (16), who showed lower baseline phosphorus levels in subjects who experienced lactate-induced panic attacks.

Of interest, the two alcoholic patients with panic disorder who had a panic attack during lactate administration had the onset of their panic disorder before the manifestation of alcoholism. This is in contrast to the five alcoholics who were not sensitive to lactate, whose panic disorder developed after their alcoholism. This differential effect between those who developed panic before or after meeting the diagnostic criteria for alcoholism supports our original hypothesis that if alcoholism gives rise to panic disorder, the pathophysiology may be different. It should be noted that most of our alcoholics with panic disorder were men and that most of our nonalcoholic patients with panic disorder were women. This resulted from an inability to find men with panic disorder with a positive family history for alcoholism who did not themselves meet criteria for alcoholism. The groups were not matched for gender, but a recent study (17) suggested that gender is not an important factor in determining response to lactate administration. By using nonalcoholic patients with panic disorder who had a family history of alcoholism as a comparison group, we were able to demonstrate that the lower level of responsiveness to lactate found in our alcoholics with panic disorder was not due to a positive family history for alcoholism. The incidence of lactate-induced panic in our nonalcoholic patients with panic disorder who had a positive family history of alcoholism was the same as previously reported in patients with panic disorder (5–7).

In conclusion, we found that alcoholics with panic disorder showed a much lower than expected incidence of panic attacks in response to lactate administration. The reason for this finding is unknown, but it suggests that these patients may have a psychobiological variant of panic disorder. Additional studies are needed to replicate and expand on this finding. Future studies on panic disorder need to evaluate the patient samples carefully for the diagnosis of past or present alcoholism and observe any dissimilarities in those who have a dual diagnosis of panic disorder and alcoholism.

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A Polysomnographic and Clinical Report on Sleep-Related Injury in 100 Adult Patients

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In 100 consecutive adults who came to a sleep disorders center complaining of repeated nocturnal injury, polysomnographic study identified five disorders: night terrors/sleepwalking (N=54), REM sleep behavior disorder (N=36), dissociative disorders (N=7), nocturnal seizures (N=2), and sleep apnea (N=1). Ninety-five patients sustained ecchymoses, 30 had lacerations, and nine had fractures. DSM-III *axis I disorders (past or current) were found in 48.1% of the group with night terrors/sleepwalking and in 30.6% of the group with REM sleep behavior disorder; these were mainly affective disorders. In these two groups, clonazepam controlled the symptoms of 51 of the 61 patients to whom it was given.*

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To our knowledge, results of an extensive polysomnographic investigation focused exclusively on sleep-related injury have not previously been published. Polysomnographic studies of night terrors and sleepwalking—which arise from non-REM sleep—have included several subjects with injurious behaviors (1–4). In a series of 23 patients with REM sleep behavior disorder documented by polysomnographic monitoring, 19 had sleep injury (5–7). We now report the results of a polysomnographic and clinical study of nocturnal injury.

METHOD

During a 6-year period, we studied 100 consecutive adult patients who presented with a chief complaint of repeated nocturnal injury to themselves and/or their bed partners. Eighty-six percent of the patients were routine referrals from physicians to our sleep disorders center, which evaluates more than 1,000 patients each year, and 14% of the patients presented as a result of media attention to reports on REM sleep behavior disorder (5, 6). All of the patients gave informed consent to participate in the study. Polysomnographic data were obtained by a protocol that used standard methods for recording and scoring (8).

Patients slept overnight in the laboratory during their usual hours. Polysomnographic monitoring included an electro-oculogram, EEG, electromyogram (EMG) (chin, bilateral anterior tibialis muscle, and extensor digitorum muscle), ECG, and nasal-oral thermocoupled airflow. There was full respiratory monitoring (impedance plethysmography and oxygen saturation by ear oximetry) of patients who had histories suggestive of disordered breathing during sleep or snoring or abnormal airflow during polysomnographic studies. On the first night, a nine-channel scalp EEG montage was used, with a paper speed of 15 mm/sec; this was increased to 30 mm/sec for 5 minutes during each hour. The subjects were continuously videotaped. Seventy-nine of the patients had two or more consecutive overnight polysomnographic studies, and 21 had one study.

A Multiple Sleep Latency Test (9) was administered to patients with suspected excessive daytime sleepiness. The patients discontinued all psychotropic medications for at least 10 days before the polysomnographic study, except for two patients who were taking lithium and one each taking phenelzine, perphenazine, and thiothixene.

Clinical evaluation consisted, first, of a standard questionnaire covering lifetime sleep/wake, medical, neurologic, and psychiatric history and a review of systems. The questionnaire contained 31 questions on medication/substance use and nine questions from the Michigan Alcoholism Screening Test (10). Past medical records were inspected. Laboratory tests, such as urine toxicology screens, were ordered as indicated. All patients found to have REM sleep behavior disorder underwent a comprehensive neurologic evaluation, as did other patients whose histories or screening neu-

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rologic examinations raised suspicions of neurologic disorder.

Before the polysomnographic studies and psychometric testing, psychiatric interviews were conducted by two of us (85 by C.H.S.; 15 by T.D.H., Accredited Clinical Polysomnographer; interrater reliability was not established) using a checklist of *DSM-III* criteria for establishing axis I diagnoses. One interviewer diagnosed axis I disorders in 41.2% (N=35) of 85 of the patients, and the other interviewer in 60.0% (N=9) of 15 patients. The patients' MMPI scores were interpreted as part of routine clinical work by an experienced staff psychologist who knew only the age, sex, and referral source for each patient but was blind to the existence of our study and to the medical record. The Beck Depression Inventory and the SCL-90 (11) were offered to the final 66 patients.

RESULTS

Polysomnographic and Clinical Data

Tables 1–3 summarize the findings. Ninety-one of the 100 patients were segregated by distinct, positive polysomnographic criteria into five diagnostic categories: 1) night terrors/sleepwalking (complex and/or vigorous behaviors appearing during abrupt arousals from non-REM sleep), 2) REM sleep behavior disorder (loss of EMG atonia with excessive limb jerking and complex or vigorous behaviors during REM sleep), 3) dissociative disorders (sequences of altered behaviors appearing during EEG wakefulness), 4) nocturnal seizures, and 5) sleep apnea/periodic movements. For the remaining nine patients, the normal (or negative-yield) polysomnographic study results were very useful in supporting the presumptive clinical diagnoses by excluding various alternative diagnoses. Major gender and age differences were revealed by the predominance of men with night terrors/sleepwalking and REM sleep behavior disorder, the predominance of women with dissociative disorders, and the late age at onset of REM sleep behavior disorder. Lacerations were often severe and required up to 40 sutures to repair. Injuries included fractures of digits, the ulna, ribs, the cervical spinous process, and the odontoid process of the second cervical vertebra that required neurosurgical intervention. There was typically a long delay from onset to diagnosis and treatment, with a range of 2 months to more than 40 years.

Night terrors/sleepwalking (N=54). Although night terrors and sleepwalking are typically considered to be disorders of childhood, in this series 33.3% (N=18) of the patients were more than 16 years old at the onset of their disorders, with a range of 3–58 years. Of these 54 patients, 87.0% (N=47) were employed, were students, or were retired. Twenty-nine (53.7%) of the patients had repeatedly fallen out of bed or run into walls and furniture, 10 (18.5%) had jumped out of windows, 10 (18.5%) had left the house and driven automobiles, wandered around streets, walked into lakes, or climbed ladders, and four (7.4%) had wielded weapons such as loaded shotguns. Injury resulted from either frenzied activity or impaired judgment. Many patients reported fragmented, precipitous images (e.g., a fire, bright light, looming figure, or collapsing roof that prompted immediate escape) or, often, more elaborate and conventional dreamlike mentation with their nocturnal episodes. In the 15 patients with histories of alcohol or substance abuse, the mean±SD length of abstinence before the polysomnographic study for the 11 patients in remission was 5.1±3.3 years.

Polysomnographic studies either established the diagnosis or supported the clinical diagnosis in 90.7% (N=49) of the 54 cases. Abnormal arousals occurred from delta wave (stages 3 and 4) non-REM sleep exclusively in 30.6% (N=15) and from multiple non-REM stages in 69.4% (N=34) of these 49 cases. The statistically significant night 2 versus night 1 differences noted in table 2 are consistent with a "first night" effect (12, 13), although these differences were not considered clinically relevant. Furthermore, the night 2 versus night 1 arousal counts listed in a footnote to table 1 did not differ significantly, thereby eliminating any possible first night effect as the cause for the large number of unexplained abrupt arousals. This finding supports the concept of night terrors and sleepwalking as "disorders of arousal" (14, 15). Nevertheless, sleep architecture and customary cycling among sleep stages were preserved (table 2). Excessive EMG twitching during REM sleep, associated with nonvigorous behaviors, was present in 10.2% (N=5) of the 49 cases, raising the possibility of mixed night terrors/sleepwalking and REM sleep behavior disorder diagnoses, although night terrors/sleepwalking was considered the predominant diagnosis because of the greater complexity and vigor of behaviors arising from non-REM sleep than from REM sleep. A Multiple Sleep Latency Test was administered to 21 (38.9%) of the 54 patients; the results of four (19.0%) were abnormal, with a mean sleep latency of less than 5.5 minutes (three with REM-onset naps, diagnostic of narcolepsy).

A representative case vignette was provided by the wife of a patient who had diagnostic polysomnographic studies.

> He seems to have the strength of 10 men and shoots straight up from bed onto his feet in one motion. He's landed clear across the room on many occasions and has pulled down curtains (bending the rods), upset lamps, and so forth. He's grabbed me and pulled on me, hurting my arms, because he's usually dreaming that he's getting me out of danger of some sort (usually something falling on us). He's landed on the floor so hard that he's injured his own body. The description "vaults explosively" describes it most clearly. There are low windows right beside our bed and I'm afraid he'll go through them some night.

TABLE 1. Characteristics of 100 Consecutive Adult Patients With Injurious Nocturnal Behaviors

Finding	Total (N=100)	Night Terrors/ Sleepwalking (N=54)	REM Sleep Behavior Disorder (N=36)	Dissociative Disorders (N=7)	Nocturnal Seizures (N=2)	Sleep Apnea/ Periodic Movements (N=1)
Sex of patient						
Male						
N	71	33	35	1	1	1
%	71.0	61.1	97.2	14.3	50.0	100.0
Female						
N	29	21	1	6	1	0
%	29.0	38.9	2.8	85.7	50.0	0.0
Ratio (M/F)	2.4/1.0	1.6/1.0	35.0/1.0	0.2/1.0	1.0/1.0	—
Nocturnal injuries						
Ecchymoses						
N	95	53	32	7	2	1
%	95.0	98.1	88.9	100.0	100.0	100.0
Lacerations						
N	30	10	12	5	2	1
%	30.0	18.5	33.3	71.4	100.0	100.0
Fractures						
N	9	3	5	1	0	0
%	9.0	5.6	13.9	14.3	0.0	0.0
Age at onset (years)						
Mean	31.2	5.1	57.4	21.5	15.5	77.0
SD	23.6	10.3	13.6	4.6	0.7	0.0
Range	3–77	3–58	13–73	12–27	15–16	—
Age at presentation (years)						
Mean	43.9	31.5	65.2	28.9	25.5	79.0
SD	19.7	9.9	11.2	6.3	10.6	0.0
Range	18–79	18–68	21–77	19–36	18–33	—
Interval from onset to diagnosis (years)						
Mean	12.7	16.4	8.2	7.4	10.0	2.0
Polysomnographic studies established diagnosis						
N	65	23[a]	36	3	2	1
%	65.0	42.6	100.0	42.9	100.0	100.0
Polysomnographic studies strongly supported clinical diagnosis						
N	26	26[b]	—	0	—	—
%	26.0	48.1	—	0.0	—	—
Positive yield of diagnoses from polysomnographic studies						
N	91	49[c]	36	3[d]	2	1
%	91.0	90.7	100.0	42.9	100.0	100.0

[a] Night terrors/sleepwalking appeared spontaneously in 21 patients and was buzzer-induced in two patients.

[b] In the 22 patients who had two consecutive polysomnographic studies, the mean±SD arousal count for night 2 was 104.7±39.1 and for night 1 it was 103.2±48.9. The mean difference (night 2 minus night 1) was 1.5±33.8 (t=0.23, df=21, n.s., paired t test with repeated measures).

[c] Five of 54 were diagnosed as having night terrors/sleepwalking on the basis of compelling history, absence of daytime dissociative disorders, and normal polysomnographic study results (which render REM sleep behavior disorder, seizures, and sleep apnea highly unlikely).

[d] Four of seven were diagnosed as having nocturnal dissociative disorders on the basis of having daytime dissociative disorders and normal polysomnographic study results.

REM sleep behavior disorder (N=36). Of the patients with this diagnosis, 86.1% (N=31) were married; the mean±SD duration of the marriages was 36.6±13.9 years. A nocturnal prodrome with a mean±SD length of 27.0±10.6 years (range=10–63) was reported by 33.3% (N=12) of these patients. Onset of the disorder was heralded by violent, dream-enacting behaviors such as throwing punches, kicking, and leaping out of bed, usually more than 2 hours after the onset of sleep. The syndrome involved sleep talking/shouting and also limb twitching and jerking without injury. Before these patients were referred, their REM sleep behavior disorder had been frequently misdiagnosed as having an epileptic or psychiatric origin, and ineffective treatments had been instituted. Polysomnographic findings in REM sleep behavior disorder have previously been reported in detail (5–7). A Multiple Sleep Latency Test was completed by 75.0% (N=27) of these 36 patients; 92.6% (N=25) showed normal results. Obstructive sleep apnea with minimal oxygen desaturation was found in 11.1% (N=3) of the 27 patients.

A REM sleep behavior disorder case vignette in-

TABLE 2. Sleep Architecture Measures of 90 Consecutive Adult Patients With Night Terrors/Sleepwalking or REM Sleep Behavior Disorder

Measure	Night Terrors/ Sleepwalking (N=54; 95 studies)[a]		REM Sleep Behavior Disorder (N=36; 67 studies)[b]	
	Mean	SD	Mean	SD
Sleep latency (minutes)[c]	19.6	16.2	31.8	32.1
REM latency (minutes)	98.0	48.7	85.4	46.2
Total sleep time (minutes)	426.3	92.9	392.4	78.1
Percent sleep efficiency (minutes asleep divided by minutes in bed)	87.2	8.6	79.1	11.7
Stage 1 percent of total sleep	6.5	8.8	10.2	12.9
Stage 2 percent of total sleep	53.0	8.1	49.7	11.6
Stages 3 and 4 percent of total sleep	19.4	7.6	19.6[d]	6.9
REM percent of total sleep	21.1	6.3	20.5	6.8

[a] Forty-one patients were studied on consecutive nights and 13 on a single night. For the 41 patients with consecutive-night studies, paired t tests with repeated measures yielded significant differences (night 2 minus night 1) for sleep latency (mean±SD=−5.7±15.0 minutes, $t=-2.43$, $df=40$, $p<0.05$); total sleep time (27.6±78.6 minutes, $t=2.25$, $df=40$, $p<0.05$); stage 1 percent of total sleep (−1.4%±3.6%, $t=-2.47$, $df=40$, $p<0.05$); stage 2 percent of total sleep (−2.9%±7.0%, $t=-2.69$, $df=40$, $p<0.05$); and REM percent of total sleep (2.4%±6.2%, $t=2.48$, $df=40$, $p<0.05$).

[b] Thirty-one patients were studied on consecutive nights and five on a single night. For the 31 patients with consecutive-night studies, paired t tests with repeated measures yielded significant differences (night 2 minus night 1) for REM latency (mean±SD=−28.9±49.4 minutes, $t=-3.26$, $df=30$, $p<0.01$); stage 1 percent of total sleep (−1.5%±3.9%, $t=-2.16$, $df=30$, $p<0.05$); stage 2 percent of total sleep (−3.7%±9.7%, $t=-2.20$, $df=30$, $p<0.05$); and REM percent of total sleep (4.2%±6.6%, $t=3.52$, $df=30$, $p<0.01$).

[c] The interval from "lights out" to the onset of 5 consecutive minutes of sleep.

[d] There was an elevated percent of stages 3 and 4 sleep for age in the group with REM sleep behavior disorder, which consisted almost exclusively of older men.

volves a 67-year-old man who was awakened one night by his wife's yelling as he was choking her. He was dreaming of breaking the neck of a deer he had just knocked down. This patient had tied himself to his bed with a rope at night for 6 years as a protective measure, owing to repeated episodes of jumping from bed and colliding with furniture and walls.

Dissociative disorders (N=7). This subgroup of patients had severe psychopathology. The lone male patient was 19 years old, with a 4-year history of twice-weekly nocturnal episodes in which he crawled around the house for 1–2 hours while growling and hissing. He had been injured while biting objects and while attempting to lift a table or bed with his jaw. He was completely amnestic for these behaviors but often recounted detailed "dreams" in which he had assumed the identity and behaviors of a large cat in a zoo. He was thought to have multiple personality disorder with exclusively nocturnal expression. Two typical episodes were recorded in the sleep laboratory, both of which

TABLE 3. Psychiatric and Neurologic Disorders Clinically Identified in 97[a] Adult Patients With Sleep-Related Injuries Who Underwent Polysomnographic Study

Item	Night Terrors/Sleepwalking (N=54)		REM Sleep Behavior Disorder (N=36)		Dissociative Disorders (N=7)	
	N	%	N	%	N	%
Patients with *DSM-III* axis I diagnoses at time of study						
Total	26	48.1	11	30.6	7	100.0
Active	19	35.2	6	16.7	7	100.0
In remission	7	12.9	5	13.9	0	0.0
Patients with diagnoses of affective disorders						
Total	17[b]	31.5	7[c]	19.4	6[d]	85.7
Active	14	25.9	5	13.9	4	57.1
In remission	3	5.4	2	5.5	2	28.6
Patients with diagnoses of alcohol/ substance abuse						
Total	15	27.8	5	13.9	3	42.9
Active	4	7.4	0	0.0	0	0.0
In remission	11	20.4	5	13.9	3	42.9
Total axis I diagnoses	54[e]	—	16[f]	—	26[g]	—
Patients with psychiatric disorders apparently etiologically associated with sleep disorder	—[h]	—	3[i]	8.3	—	—
Patients with neurologic disorders apparently etiologically associated with sleep disorder	4[j]	7.4	9[k]	29.0	—	—

[a] From the series of 100 patients with sleep-related injury, three patients with nocturnal seizures or sleep apnea were excluded from this analysis.

[b] Recurrent major depression (N=12), dysthymic disorder (N=7), bipolar disorder (N=3), and adjustment disorder (N=1): 23 affective disorders in 17 patients.

[c] Recurrent major depression (N=5) and adjustment disorder (N=2).

[d] Major depression (five recurrent, one single episode) and dysthymic disorder (N=3): nine affective disorders in six patients.

[e] Remaining diagnoses: anxiety disorders (N=7), eating disorders (N=2), dissociative disorder (N=1), and schizophrenia (N=1).

[f] Remaining diagnoses: anxiety disorder (N=3) and intermittent explosive disorder (N=1).

[g] Remaining diagnoses: dissociative disorder (seven patients: psychogenic amnesia [N=6], fugue [N=3], nocturnal multiple personality disorder [N=1]), eating disorder (N=2), attention deficit disorder (N=1), and somatoform disorder (N=1).

[h] Indeterminate associations by history.

[i] Two cases emerged concurrently with an adjustment disorder induced by divorce or by auto accident, and one chronic case emerged with abstinence from longstanding ethanol/amphetamine abuse.

[j] Night terrors/sleepwalking emerged with closed head injury (N=2), encephalitis (N=1), and stroke (N=1).

[k] REM sleep behavior disorder emerged with dementia (N=5), stroke (N=2), olivopontocerebellar degeneration (N=1), and Parkinsonism (N=1). Five cases in which the neurologic disorder had an uncertain association with REM sleep behavior disorder were excluded from the analysis.

arose from EEG wakefulness. Polysomnographic studies were diagnostic for two other patients; in the remaining four patients, polysomnographic studies detected no abnormality, but each patient had an extensive history of diurnal dissociative disorders.

Nocturnal seizures (N=2). One of the patients with this diagnosis was an 18-year-old man who had a 3-year history of progressively extreme sleep violence in which he would shout, thrash his limbs violently, run around the house, and pull doors off their hinges. Five polysomnographic studies documented numerous violent episodes associated with EEG spike and paroxysmal rhythmic activity arising from all stages of sleep. The second patient was a 33-year-old woman with a 17-year history of left-side shaking movements and falling out of bed during the terminal stages of sleep. A polysomnographic study documented seven clinical seizures during stage 2 non-REM sleep that consisted of left-side dystonia and limb jerking. There were EEG spike and slow wave complexes, maximal over the right frontocentral region, accompanying these clinical events.

Obstructive sleep apnea and periodic movements (N=1). The 79-year-old man with this diagnosis had a 2-year history of injurious, dream-enacting behaviors that appeared to result from abrupt, apnea-induced arousals from REM sleep. Polysomnographic studies revealed obstructive apneas with oxygen desaturations reaching a nadir of 80% during REM sleep. He also had periodic movements during non-REM sleep at a frequency of 112 per hour.

Psychometric Data

Night terrors/sleepwalking. For the night terrors/sleepwalking group, there was a 75.9% (41 of 54) MMPI completion rate with five profiles that were not valid, yielding 36 usable profiles. Twenty-three (63.9%) were abnormal; depression was detected in 13 (56.5%) and personality disorder (mainly passive-aggressive and impulsive) in 12 (52.2%). Ten patients with clinical depression at the time of polysomnographic study completed an MMPI, and their mean±SD depression scale T score was significantly higher than that of 25 patients without clinical depression at the time of study (77.1±10.5 and 58.1±13.8, respectively; $t=3.91$, $df=33$, $p<0.01$). The mean Beck depression score for the 33 patients who completed that test was 6.4±7.4; eight patients who were clinically depressed at the time of polysomnographic study had significantly higher scores than 25 patients who were not depressed at that time (16.0±8.2 and 3.4±3.5, respectively; $t'=4.22$, $p<0.01$, comparison of means assuming unequal variances, df not specifically fixed in this procedure [16]). The mean±SD SCL-90 total scores and subscale scores for each of the 31 patients who completed that test ranged from 0.21±0.47 to 0.59±0.69, with significantly higher mean depression subscale scores for six clinically depressed patients than for 25 nondepressed patients at the time of polysomnographic study (1.7±0.8 and 0.33±0.3, respectively; $t'=3.99$, $p<0.05$, df not fixed [16]).

REM sleep behavior disorder. There was a 92.3% MMPI completion rate (N=24) for the 26 patients offered the test; 10 patients were excluded because of neurologic impairment or illiteracy. Eleven of the 24 (45.8%) had abnormal profiles (somatization in 10 and depression in eight). Personality disorder was not suggested by the MMPI results of any patient. The mean Beck depression score for the 17 patients who completed that test was 6.5±4.5. The mean SCL-90 total score and subscale scores ranged from 0.2±0.4 to 0.8±0.9; the mean depression score was 0.5±0.6 and the mean anger-hostility score was 0.2±0.2. These Beck and SCL-90 scores are within normal limits.

Treatment

Clonazepam was prescribed for 51.9% (N=28) of the 54 night terrors/sleepwalking patients with the most vigorous or dangerous nocturnal behaviors and also for 91.7% (N=33) of the 36 patients with REM sleep behavior disorder. Rapid and sustained control of sleep injury was achieved for up to 6 years in 83.6% (N=51) of the 61 patients in these combined groups. The dose range was 0.25–2.00 mg nightly. Taking clonazepam 1–2 hours before retiring can prevent episodes that emerge shortly after sleep onset. There was minimal development of dosage tolerance over time, and no instance of medication abuse. Self-hypnosis was taught to and used by 40.7% (N=22) of the 54 night terrors/sleepwalking patients; 63.6% (N=14) of these 22 patients achieved substantial benefit. The nonresponders generally had more severe night terrors/sleepwalking disorders. The two patients with nocturnal seizures achieved full benefit from anticonvulsant therapy (sodium valproate or carbamazepine).

DISCUSSION

These data demonstrate the necessity of extensive polysomnographic study in diagnosing the cause of sleep-related injury. Ninety of the 100 patients had night terrors/sleepwalking or REM sleep behavior disorder, which are categories of parasomnias defined as abnormal physical events emerging during arousal from sleep or occurring within sleep (15). The present report expands the known polysomnographic and clinical features of these two parasomnias.

Night terrors and sleepwalking have traditionally been regarded as disorders of abrupt arousal from delta wave non-REM sleep during the first third of the sleep cycle, rarely accompanied by detailed mentation and predominantly affecting children, who scream with terror and/or sit up, leave their beds, and engage in simple or complex activities with subsequent amnesia (1, 14, 15, 17–19). Our findings in adults suggest that all non-REM sleep stages are commonly involved in night terrors/sleepwalking, although there is a special vulnerability during delta wave non-REM sleep for undetermined reasons. Contrary to conventional teaching, elaborate dreamlike mentation can also be present, along with substantial recall of nocturnal behaviors, at least in adults. Excessive EMG twitching with gross behaviors during REM sleep was also seen in five of the patients with night terrors/sleepwalking. Therefore, a spectrum of REM and non-REM motor parasomnias is suggested by the data, with REM sleep behavior disorder and the traditional form of night terrors/sleepwalking being points of reference for a range of abnormal polysomnographic and clinical states across the sleep cycle and the life cycle.

The literature on psychopathology in adult night terrors/sleepwalking rarely contains polysomnographic documentation (2, 4, 20–23). In two MMPI and psychiatric interview studies, without polysomnographic confirmation, of 40 subjects with active night terrors and 29 with active sleepwalking who were recruited by advertisement, more than 70.0% had histories of dangerous sleep behaviors (20, 21). Eighty-five percent of the night terrors group were diagnosed—without stated diagnostic criteria—as having "neurosis" or personality disorders; 72% of the sleepwalking group were assigned a diagnosis—also without listed criteria—which was usually personality disorder. These reports have served to promulgate the viewpoint that most adults with night terrors/sleepwalking have psychopathology (24, 25) and that "insight-oriented psychotherapy is the treatment of choice" for these parasomnias (25). Our findings, at least in reference to injurious night terrors/sleepwalking, do not support these positions, although the basis for assessing psychopathology in our study (*DSM-III* axis I diagnoses from interview and history; personality disorder from MMPI interpretation) was not identical to that of previous studies.

The data in this report allow some conclusions concerning adults with injurious night terrors/sleepwalking. 1) There are, typically, abrupt arousals throughout the night from any stage of non-REM sleep, linked with anxiety and/or motor activation that can be slow, lengthy, and complex or short and frenzied (with either extreme being potentially lethal). 2) Axis I psychiatric disorders are present in almost half the cases, particularly depression with active symptoms (recurrent major depression, dysthymic disorder, adjustment disorder) or alcohol/substance abuse in remission. However, we must emphasize that more than 50% of the patients had never had an axis I disorder, only 35.2% (19 of 54) had an active axis I disorder at the time of polysomnographic study, and nearly all exhibited a high level of psychosocial functioning. 3) Successful treatment of depression or long-term abstinence from substance use does not ensure remission of night terrors/sleepwalking. Therefore, direct intervention, as with clonazepam therapy or hypnosis, seems highly desirable.

We believe that the health risk is substantial for adults who injure themselves during night terrors/sleepwalking. If initial intervention for an accompanying psychiatric disorder does not control the night terrors/sleepwalking within a matter of days (or weeks, at the very most), adjunctive treatment with clonazepam or hypnosis should be started. Eventual remission of a psychiatric disorder may afford the opportunity to discontinue clonazepam to determine whether the night terrors/sleepwalking has also remitted. The extent of association and covariance between affective disorders and night terrors/sleepwalking is unknown; thus, separate treatments may often be required for these separate though possibly related conditions. The finding that more than half of our total night terrors/sleepwalking sample had no axis I disorder and that two-thirds had no personality disorder by MMPI analysis (24 of the 36 completed tests) indicates that a substantial subgroup of these patients have an unexplained physiologic predisposition to this parasomnia. These findings further justify a symptomatic approach in order to directly manage the risk of injury. It should be noted that there are no data on the spontaneous remission rate of either injurious or noninjurious adult night terrors/sleepwalking.

Clonazepam proved to be a rapidly effective and lasting treatment for the patients in this study, which provides added support for the anecdotal literature on the efficacy of benzodiazepines, particularly diazepam, in night terrors/sleepwalking (2, 3, 23, 26–33). Since the natural history of adult night terrors/sleepwalking is unknown, our strategy is to recommend yearly drug holidays to determine the need for ongoing treatment.

REM sleep behavior disorder was described in 1986 (5) as a new category of parasomnia associated with neurologic disorders and with advanced age in men. However, more recent reports (34, 35) and also findings from this series suggest that adverse life events resulting in adjustment disorders or posttraumatic stress disorder can herald the onset of REM sleep behavior disorder. Thus, a psychophysiologic subgroup of REM sleep behavior disorder may exist. Furthermore, protracted REM sleep behavior disorder may be associated with discontinuation of REM sleep-suppressing agents (35).

Diagnostic criteria for REM sleep behavior disorder have been defined (7) and include a history of injurious or disruptive sleep behaviors (usually associated with dreams that are excessively vivid, action-filled, and violent) together with polysomnographically documented loss of the customary EMG atonia and emergence of complex and/or vigorous behaviors during REM sleep. Comprehensive neurologic evaluations were completed on all of our patients with REM sleep behavior disorder because of the high prevalence of neurologic disorders in our initial sample (5, 6) and because of a neurologic animal model of REM sleep behavior disorder that was produced by experimental lesions applied to the pontine tegmentum (36–38). Experience with human REM sleep behavior disorder has revealed that a variety of pathologic processes (neurologic and psychiatric) can disrupt atonia during

REM sleep and allow the release of dangerous behaviors. We had previously identified clonazepam as an effective therapy for REM sleep behavior disorder, and this experience served as the basis for using clonazepam in injurious night terrors/sleepwalking.

The two cases of nocturnal seizures reemphasize the importance of extensive polysomnographic study in evaluating harmful sleep behaviors. Besides frank seizure disorder, illustrated by these two cases, other potentially dangerous sleep-related conditions that are responsive to anticonvulsant medications have been described: 1) hypnogenic paroxysmal dystonia, characterized by tonic spasms and violent movements during non-REM sleep, normal EEGs, presence in all age groups, and responsivity to carbamazepine (39); 2) episodic nocturnal wandering, with high response rate to anticonvulsant therapy but with infrequent EEG abnormalities (40, 41); and 3) poststroke paroxysmal nocturnal disorder, with nightmares and agitated behavior controlled by phenytoin but not by two benzodiazepines (42).

The only dissociative disorder in the official sleep nosology that is recognized in the differential diagnosis of sleepwalking is fugue state (14). One abstract (43) and data from this report, documented by polysomnographic studies, indicate that sleep-related psychogenic amnesia and multiple personality disorder must be added to this list.

Finally, besides the single case in this series of sleep apnea presenting as injurious, dream-enacting behaviors, there is recognition that apnea can be accompanied by agitation and ambulation resulting from delirious arousal (44).

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Differences Between Patient and Family Assessments of Depression in Alzheimer's Disease

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A structured interview covering the DSM-III *criteria for major depression was adapted for separate use with Alzheimer's disease patients and with their families. Data from 36 patients yielded a depression rate of 13.9%, whereas information from their families indicated that the rate was 50.0%. This disagreement reflected greater family endorsement of patients' loss of interest or pleasure, irritability, fatigue, and feelings of worthlessness. Use of* DSM-III-R *criteria narrowed but did not eliminate the discrepancy between patients' and families' assessments of the patients' depression. Uniform procedures for gathering and integrating data from the family that are relevant to diagnosis in this group are indicated.*

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Alzheimer's disease is a neurological condition marked by progressive cognitive deterioration. Dysmnesia, loss of ability to reason, and social withdrawal evolve over the course of the disease. While much attention has been focused on the confusion of dementia with depression (i.e., pseudodementia), it has been pointed out that it is more common for a patient to have both dementia *and* depression (1). The coexistence of dementia and depression poses formidable diagnostic difficulties. First, there may be an overlap between the descriptive features of the two disorders. For instance, memory dysfunction, a prominent symptom of dementia, may be present in depression (2). Social withdrawal and constriction of interest and pleasure may attend both dementia and depression.

A second impediment to accurate diagnosis is the effect of cognitive dysfunction on the ability of a dementia patient to provide an accurate or thorough history. For instance, a patient might not be able to recall disturbances in sleep, interest, or appetite that are well-known to others. In addition, a moderately demented patient may remain mute or provide responses that are not related to the question asked. Repetition of the question or gentle efforts to redirect the patient may cause irritability or increasing agitation and result in termination of the interview. To compensate for these limitations in gathering history, it is standard clinical practice to augment information obtained from the subject with collateral information from sources knowledgeable about the patient's behavior—usually, family members.

Availability of collateral information is critical in evaluating a person with dementia, since the patient may be substantially unable to provide a complete or accurate history. However, the contribution that outside sources make to a clinical diagnosis is rarely quantified and may vary widely from patient to patient or over time in the same case. It is implicitly assumed that variation in the share of the psychiatric history provided by an informant does not change the diagnostic outcome. This assumption, however, may be erroneous. For instance, the sensitivity of collateral sources to certain data may be different from that of the patient. Such a discrepancy could change the frequency with which specific diagnoses are made, as a function of dependence on collateral input. It could also confound outcome studies by introducing a bias over time if reliance on collateral sources changes as a given individual's cognitive function worsens. The current study was aimed at comparing the occurrence of depression in patients according to information provided by the patients themselves and according to information supplied by their families.

METHOD

The subjects were 46 outpatients (28 women and 18 men), referred by community and medical sources to the Dementia Clinic of the University of Minnesota Hospital and Clinic (3) for evaluation between April 1986 and May 1987, who satisfied the criteria of Mekhann et al. (4) for probable or possible Alzheimer's disease. In all cases the patients had clear histories of cognitive dysfunction of at least 1 year's duration that were confirmed by reliable informants. The patients' mean±SD age was 72.9±8.5 years (range=

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54–94). All patients were evaluated by a neurologist (D.S.K.) and a psychiatrist (T.B.M.). Patients with neurological findings indicative of a disorder other than Alzheimer's disease (i.e., abnormalities in strength, coordination, sensation, reflexes, or gait) were excluded from the study. Families were separately interviewed by a psychologist (W.N.R.) blind to the outcome of the patients' interviews. Workup of each patient included administration of the Mini-Mental State examination (5). The mean±SD score on the Mini-Mental State was 18.0±7.5 (range=0–30).

A 46-item structured interview was constructed for use with patients who have differing degrees of dementia; it comprehensively inquires about the presence of symptoms that meet the *DSM-III* criteria for a major depressive episode. Short, present-tense questions that directly express these criteria were formulated. Each item was phrased to elicit a response of yes or no, and 43 of the 46 items required a yes answer to register the presence of psychopathology. The usual psychometric practice of balancing normative responses between yes and no was abandoned to minimize confusion related to frequent shifts in the response required to endorse a symptom. Three nonconsecutive items—"Does life seem worthwhile?" "Do you have enough energy?" "Are you able to relax?"—required an answer of no to indicate the presence of psychopathology. In practice, all patients who answered "no" to a majority of the other items responded "yes" to the three aforementioned items. Items derived from the A criteria for the *DSM-III* diagnosis of major depressive episode (depression and/or irritability, anhedonia, or loss of interest) involved two steps: if the subject said that he or she had the symptom, a follow-up question (otherwise omitted) asked whether the symptom had been present for 2 weeks or longer. Items derived from the B criteria (appetite and weight, sleep, psychomotor activity, interest, energy, feelings of guilt or worthlessness, cognition, and suicidal thoughts or actions) did not involve a time frame. This modification of the *DSM-III* criteria was adopted to simplify the interview while preserving the duration criteria for the core symptoms.

The patients were told at the outset that they would be asked a series of questions about their "emotional well-being." Questions were asked in the same order for each person. The examiner repeated questions if necessary and provided simple cues such as alternative words for a particular symptom (i.e., "depressed" for "sad"). However, efforts to clarify the respondent's answer were not permitted. This policy was adopted to maintain the structured format, to ensure completion of the interview within 20 minutes, and to avoid calling attention to the subject's deficits and thereby provoking agitation.

The interviewer rated the patient's responses using a yes-no format. If the respondent's answer did not provide clear or meaningful information, this outcome was recorded and the next question was posed.

An additional six items required the examiner to rate the patient's appearance and behavior. These items rated evidence of diminished ability to think, concentrate, or make a decision; the presence of psychomotor agitation or retardation; and the presence of emaciation. These six items were rated on a 4-point scale ranging from strong evidence to no evidence; the rater also had the option of reporting that the evidence was conflicting or insufficient.

Since the interview was intended for use with subjects with widely differing attention spans and memory function, its length and format were designed to allow completion in less than 20 minutes. This goal was met during the clinical application of the instrument.

A family version of the same interview was constructed so that identical questions about the patient could be systematically posed to a person knowledgeable about the patient's condition.

The patient interview was administered during the afternoon of the first clinic visit following a 30-minute neurological examination. The family interview was conducted during the first clinic visit while the patient was undergoing routine studies. When the patient was accompanied by more than one relative (this occurred on three occasions), a single representative was designated to answer all questions, although he or she could consult with the others in arriving at an answer. The kinship of the respondent was recorded, and he or she was asked to complete a Beck Depression Inventory and, using a 7-point visual analogue scale, to rate 1) the patient's current mood (1=happy; 7=depressed), 2) his or her certainty about the patient's mood (1=certain; 7=uncertain), and 3) how he or she would feel "in the patient's shoes" (1=happy; 7=depressed). Finally, the respondent was asked whether the patient had a history of treatment for mental illness (yes, no), whether the patient needed treatment for depression (yes, no, unsure), and how many hours the respondent spent with the patient daily (≤16; >16).

Major depression was considered present if one or more symptoms from the A criteria had been present for 2 weeks or longer and four of the eight B criteria were endorsed.

In the statistical analysis, we used the kappa coefficient to compare agreement across observers (6). Variables were compared by means of chi-square tests with Yates' correction, two-tailed Student's t tests, and McNemar tests for the significance of changes. Statistical significance was considered to be $p \leq 0.05$.

RESULTS

Ten of the first 20 patients were selected at the convenience of the interviewers without regard to clinical status to be interviewed and rated by both T.B.M. and W.N.R. The mean rate of agreement per interview for patients' responses (yes, no, or unscorable) was 89% (range=78%–100%) and for observer-rated behaviors (present, absent) was 80% (range=57%–100%). The mean±SD kappa coefficient for patient interview items (excluding seven items not observed by either rater)

TABLE 1. Data on Patients With Alzheimer's Disease and Their Families Whose Assessments of the Patients' Depressive Symptoms Were Concordant (N=15) or Discordant (N=16)

	Concordant Group			Discordant Group			
Variable	Mean	SD	N	Mean	SD	N	Analysis
Sex of patient							$\chi^2=0.02$, df=1, p=0.88
Male	—	—	7	—	—	6	
Female	—	—	8	—	—	10	
Age of patient (years)	73.0	8.8	—	71.8	8.0	—	t=−0.39, df=29, p=0.70
Mini-Mental State score of patient	18.3	5.9	—	17.3	7.8	—	t=−0.38, df=29, p=0.71
Beck depression score of family rater	4.9	3.7	—	7.1	5.0	—	t=1.38, df=28, p=0.18
Patient interview items not scored yes or no	1.2	1.2	—	4.5	8.3	—	t=1.52, df=29, p=0.14
Family rater's estimate of patient's current mood (1=happy; 7=depressed)	3.4	1.4	—	4.1	1.1	—	t=1.61, df=29, p=0.12
Family rater's kinship with patient							$\chi^2=0.03$, df=1, p=0.86
Spouse	—	—	8	—	—	8	
Other	—	—	7	—	—	8	
Hours per day family rater spent with patient							$\chi^2=0.04$, df=1, p=0.84
≤16	—	—	7	—	—	7	
>16	—	—	8	—	—	9	
How family rater would feel if he or she had patient's condition (1=happy; 7=depressed)	5.5	1.4	—	6.1	1.4	—	t=1.05, df=29, p=0.30
Patient had history of treatment for mental disorder							$\chi^2=4.78$, df=1, p=0.03
Yes	—	—	0	—	—	6	
No	—	—	15	—	—	10	
Family rater's estimate of patient's need for treatment of depression							$\chi^2=5.11$, df=1, p=0.02
Yes or unsure	—	—	1	—	—	8	
No	—	—	14	—	—	8	
Family rater's certainty about patient's current mood (1=certain; 7=uncertain)	1.6	0.8	—	3.1	1.7	—	t=3.02, df=29, p=0.005

was 0.73±0.33 (range=0–1.00), and the kappa coefficient for overall interrater agreement on the presence or absence of depression was 0.74.

Overall, 15.2% (seven of 46) of the patients satisfied the *DSM-III* criteria for major depression on the basis of the patient interview data. The Mini-Mental State score for the depressed subjects (mean±SD=20.7±9.4) was not significantly different from the score for those who were not depressed (17.6±7.2).

Thirty-six subjects were accompanied to the clinic by relatives familiar with their behavior. Both individual and family evaluations were completed on this group. On the basis of the patient interviews, five of these 36 patients (13.9%) met the criteria for major depression. In contrast, 50.0% (18 of 36) of the patients met these criteria when family interview scores were used. There was no significant difference in Mini-Mental State score between the 18 patients who were rated depressed (mean±SD=16.9±8.7) and the 18 rated not depressed (19.0±5.5) by their families. The difference between meeting the criteria for diagnosis according to the patient interview data and according to the family interview data was statistically significant (McNemar test, $\chi^2=7.58$, df=1, $p<0.01$). The family and the patient disagreed in 53% (19 of 36) of the cases. The great majority (16 of 19) of the disagreements involved a patient saying that he or she was not depressed, whereas the family provided information to the contrary. Three cases involved disagreement in which the patient acknowledged depression and the family did not. We felt that the low number of the latter cases precluded further analysis. Thus, the term "discordant" as used in the remainder of this article refers to the 16 cases in which the family endorsed symptoms of depression and the patient did not. The term "concordant" refers to the 15 cases in which the family and patient agreed that the patient was not depressed. There were only two cases in which the family and the patient agreed on the presence of depression.

Discordant cases were compared with concordant cases across a number of independent variables (see table 1). The groups differed significantly on three variables: 1) patients in discordant cases were more likely to have histories of treatment for mental illness, 2) family raters in discordant cases were less certain of their assessments of the patients' current mood, and 3) family raters in discordant cases were more likely to

TABLE 2. Symptoms of Depression in Alzheimer's Disease That Were Rated Present by the Family but Not by the Patient

	Discordant Cases (N=16)	
Symptom	N	%
Loss of interest or pleasure in usual activities	12	75.0
Irritability for at least 2 weeks[a]	11	68.8
Overly tired	10	62.5
Loss of interest in almost everything for at least 2 weeks[a]	10	62.5
Loss of pleasure in everything for at least 2 weeks[a]	10	62.5
Sad mood for at least 2 weeks[a]	7	43.8
Feeling worthless	7	43.8
Lack of energy	7	43.8
Middle insomnia	6	37.5
Excessive sleeping	5	31.3
Increased appetite	4	25.0
Trouble thinking clearly	4	25.0
Trouble making a decision	4	25.0
Weight loss	3	18.8
Thoughts of death	3	18.8
Loss of libido	2	12.5
Late insomnia	2	12.5
Anorexia	2	12.5
Initial insomnia	2	12.5
Trouble concentrating	2	12.5
Guilt	1	6.3
Weight gain	1	6.3
Suicide attempt	0	0.0

[a] *DSM-III* A criterion for major depressive episode.

profess uncertainty about whether the patients needed treatment for depression.

For each *DSM-III* symptom, the percentage of patients in the discordant group (N=16) in which the family endorsed that symptom and the patient did not was calculated (see table 2). The higher the percentage, the more often a specific item contributed to a discordant diagnostic outcome (i.e., the patient said he or she was not depressed and the family said depressed). Items related to A criteria were the most likely to be endorsed by the family and not by the patient.

DISCUSSION

Estimates of the occurrence of depression in Alzheimer's disease range from 12.7% (7) to 57% (8). This variance may be partially attributable to differences in recruitment practices, assessment methods, diagnostic criteria, and length of follow-up as well as in lifetime versus point-prevalence estimates. Most studies of depression in Alzheimer's disease have gathered information from the family as part of the evaluation. However, only Burke et al. (9) seem to have kept data from the patient and from the family segregated. It is possible that differences in the rate of depression in Alzheimer's disease across studies are partially due to different policies on the collection and integration of family data in the diagnostic process. In the sample we studied, the rate of depression rose nearly fourfold (from 13.9% to 50.0%) if diagnosis based on data from the patient interview was replaced with diagnosis based on information supplied by the family. We maximized this difference by designing the study so that data were gathered separately, thus preventing consultation between patient and family, and by preventing interviewers from clarifying ambiguous answers. Even if these strict methods had only doubled the rate of discordance, the difference would still have been sufficiently great to cause a significant variance in the prevalence of depression.

Analysis of the specific areas of disagreement between the discordant patients and families indicated that loss of interest in usual activities, irritability, being overly tired, loss of interest in almost everything, and loss of pleasure in everything were the areas of greatest divergence in the ratings. This finding accords very closely with the observations of Burke et al. (9), who found that when Alzheimer patients free of affective disorder on entry into their study were followed over 34 months, at the end of the study period there were marked elevations in the endorsement by collateral sources of symptoms such as loss of interest, decreased energy, difficulty in thinking and concentrating, and psychomotor agitation or retardation. The collateral sources, as in the present study, reported more symptoms than the patients themselves. Burke et al. concluded that it was best to consider these symptoms as symptoms of dementia rather than evidence of a separate depressive syndrome. Lazarus et al. (10) also noted the difficulties in assigning etiological status to symptoms common to depression and dementia.

Constriction in sources of interest and pleasure, reduction in mobility and stamina, and feelings of being unable to contribute and being burdensome often emerge as dementia unfolds. The point at which they appear is variable and probably depends on factors such as temperament, past accomplishments, current social resources, and the rate at which the disease progresses. These symptoms may be indistinguishable from the symptoms of major depression but do not necessarily have the same etiology, natural history, or prognostic value. Relatives—especially those who are uncertain about the patient's mood state and/or need for treatment of depression and who are mindful of a history of treatment for mental disorder—endorse these symptoms and thereby provide data that meet the criteria for a major depressive episode. Relatives who are more certain of their responses and are not contending with a history of mental disorder in the patient may accept these symptoms as a part of the disease process.

While it seems probable that discordance between patient and family would be most prominent when the patient is suffering from dementia, the study design did not address this question. Since we did not study a control group, we cannot say whether the discrepancy is unique to Alzheimer's disease or is more generic, involving other conditions and age groups. However, irrespective of how widespread this phenomenon is, its implications for working with Alzheimer patients remain unchanged. The foremost of these is that the method of gathering collateral data and the scheme for integrating these data into a diagnostic formulation need to be specified. The results do not indicate which set of data should be given primacy in arriving at a diagnosis. Such guidance will require longitudinal studies that track natural history and/or treatment outcome.

It should be noted that this study did not establish the validity of the items incorporated in the patient and family interviews for the diagnosis of depression in dementia. The use of *DSM-III* criteria in almost verbatim form was considered sufficient for the purposes of establishing validity. Blazer and Williams (11) have concluded that the *DSM-III* criteria are suitable for use with elderly populations.

During the later phases of this study, *DSM-III* was replaced by *DSM-III-R*. The latter contains four changes in the criteria for a major depressive episode. First, whereas *DSM-III* listed irritability as one of the A criterion symptoms without qualification, *DSM-III-R* restricts the symptom of irritability to diagnosis of children and adolescents. Second, loss of interest or pleasure in usual activities, one of the eight B criterion symptoms in *DSM-III*, was dropped. This eliminated the redundant presence of "loss of interest" in both A and B criteria. Third, *DSM-III-R* allows the clinician to discount a symptom if it can be "established that an organic factor initiated and maintained the disturbance." Fourth, the A and B criteria are consolidated into a single A criterion in which five of nine items must be endorsed, provided that at least one of them is depressed mood or marked loss of interest or pleasure.

DSM-III-R criteria were retrospectively applied to our study data. The "loss of interest and pleasure in usual activities" item was merged with the item on loss of interest or pleasure in the A criterion. The cognitive dysfunction item was discounted, since an organic factor that could account for it was present in the form of Alzheimer's disease.

When we used the *DSM-III-R* criteria, the rate of depression for the overall sample of patients interviewed (N=46) fell from 15.2% to 4.3%. In four cases, patients who met the *DSM-III* criteria failed to meet the *DSM-III-R* criteria. For one of the four, the elimination of irritability was critical. For the other three, the elimination of cognitive dysfunction and the merger of the criteria for loss of interest or pleasure in usual activities reduced the number of symptoms below five, even though sadness or pervasive loss of interest or pleasure was present.

With respect to family reports, the rate of depression when *DSM-III-R* criteria were used fell from 50.0% to 30.6% (11 of 36 cases). Five cases meeting the *DSM-III* criteria failed to meet the *DSM-III-R* criteria. In one of these cases, neither of the mandatory symptoms (sadness or loss of pleasure or interest) was present. The other four failed because the total symptom count fell below five.

Retrospective application of *DSM-III-R* criteria resulted in a substantial reduction in the rate of depression according to both patient and family interview data. The family rate fell by about 20% and the patient rate by about 11%. This suggests that *DSM-III-R* has tightened the diagnostic boundaries for major depression in Alzheimer's disease and reduced the discordance between patient and family data. It is possible that prospective application of *DSM-III-R* criteria would result in even lower rates because of heightened recognition that additional symptoms, such as weight loss and insomnia, are secondary to Alzheimer's disease and not to major depression.

As the population ages, with the young-old and old-old accounting for increasing proportions of the population, there is clearly a need to develop more refined guidelines for the use of data from multiple sources in diagnosing depression in demented patients.

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Prevalence of Severe Mental Disorders in Disaffiliated and Homeless People in Inner Melbourne

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The authors determined the prevalence of mental illness in 382 people representative of the occupants of shelters for the homeless and cheap single-room accommodations in inner-city areas of Melbourne. Clinicians were trained to use a standardized diagnostic instrument, the Structured Clinical Interview for DSM-III-R, to diagnose a range of severe mental disorders, including psychotic, affective, and substance-related disorders. Almost half the people interviewed received diagnoses of current disorders, and over 70% received lifetime diagnoses. There was considerable comorbidity. Many factors are likely to contribute to the concentration of people with mental disorders in such homeless and disaffiliated groups.

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The increase in numbers of obviously disturbed homeless people in the cities, especially in the United States (1), has prompted several studies of mental disorder among homeless persons. Various subgroups of the homeless population have been sampled in these studies, including frequenters of skid row, patients treated in hospital emergency rooms, and occupants of single rooms. The diagnostic criteria used and skills of the interviewers have also varied (2, 3). It nonetheless appears from American and British studies that between one-quarter and one-half of adult homeless persons are suffering severe and perhaps chronic mental disorder (2–6). The number and proportion of the mentally ill appear to have increased significantly over the last 20 years, and the proportion of young chronically ill has apparently increased as the proportion of older substance abusers has decreased (6, 7).

Although postwar changes in homeless populations are commonly linked to changes in both psychiatric services and the population structure (8, 9), the risk factors for inception and maintenance of homelessness in various subgroups of the population, including those with mental disorder, remain poorly understood (10).

Previous studies of mental illness in homeless people have paid little attention to comorbidity. Comorbidity, the concurrence of two or more psychiatric disorders or of physical and psychiatric disorders in the same individual (11, 12), is gaining increasing attention in the psychiatric literature because of its relevance to treatment response and mortality. Information has also been scarce on the prevalence of substance abuse and dependence in these people (10). Recent surveys in Los Angeles (13, 14) support the widespread impression that the prevalence of such disorders and the level of comorbidity are likely to be high.

In Australia, Doutney et al. (15) diagnosed schizophrenia in 15% of men living in a shelter in central Sydney. The extent of the local problem is not otherwise documented, but members of the Victorian Council to Homeless Persons have expressed concern that staff in shelters, day centers, and other services appear to be facing increasing difficulties in dealing with homeless and disaffiliated people with apparent mental disorders.

Lack of shelter and disaffiliation, or lack of social roots in a community, are often merged in the concept of homelessness (10). While people sleeping in shelters (or crisis accommodation for the homeless) are clearly homeless, many other disaffiliated people are living in cheap single rooms. People in such marginal accommodations are probably more numerous in Melbourne than those living outdoors or in shelters, interchange

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with them to some degree, and appear to present a number of similar problems to service providers.

Although lack of shelter is an increasing problem in Melbourne, people without shelter are not encountered in the numbers known in recent times in the United States. A contributing factor may be that cheap single rooms are still more available in Melbourne, despite a shrinking supply, than in the United States (6, 16).

The aim of this survey was to estimate the prevalence of severe mental disorders, individually and in combination, in representative subgroups of the homeless and disaffiliated population of inner Melbourne, with a view to guiding modifications and additions to service provision.

METHOD

Interviewing and Diagnosis

"Severe mental disorder" was defined as a disorder that met the *DSM-III-R* criteria for schizophrenia, other psychotic disorders, major affective disorders, dysthymic disorder (which indicates unremitting depressed mood for 2 years), or substance abuse or dependence (alcohol or other). In addition, we recorded indicators of organic mental disorder.

We used modules of the Structured Clinical Interview for DSM-III-R (SCID-R) (17) to construct the primary diagnostic tool. Modules from the patient version, which allows for subcategorization of psychotic disorder, were preceded by an exploratory overview from the nonpatient version. The SCID-R is a flexible interview allowing cross-examination and use of information from all available sources. We added the Mini-Mental State examination (18), to indicate whether or not a subject was cognitively impaired, and questions on accommodation, income, and activities.

We recruited two experienced psychiatric nurses, a medical practitioner, a social worker, and two psychologists as interviewers. They spent 2 weeks being trained in use of the interview schedule by three psychiatrists (H.H., P.M., and P.B.), until an acceptable level of reliability was obtained, then conducted the interviews over 3 months in the winter of 1987. Most interviews took between 1 and 2 hours to complete. Failure to complete an interview was rare. Weekly meetings throughout this period allowed discussion and detailed supervision of the work.

One of the psychiatrists (P.B.) conducted 38 independent repeat interviews within 3 weeks of the originals to provide a measure of test-retest reliability. She was blind to the content and diagnoses of the original interviews, and the subjects were chosen randomly from each interviewer's set of respondents.

Informal consensus diagnoses of organic mental disorder were made by the same three psychiatrists. These were based on available cognitive and/or behavioral indicators from unstructured sections and exclusion items of the SCID-R, the Mini-Mental State scores, and the supervision process.

Sampling Procedures

The subjects were occupants of the Melbourne shelters for homeless people and of the special accommodation houses and low-cost rooming houses in St. Kilda. St. Kilda is a needy inner-city area of Melbourne with a high concentration of these types of accommodation. Only residents between the ages of 15 and 60 years were interviewed, and people whose command of English was inadequate to complete the survey instruments were excluded.

The three main shelters for homeless men in Melbourne are located in inner areas of the city and have a total of 670 beds. One of these shelters houses a small number of women. We also approached a small (seven-bed) shelter for women and a small youth crisis center. The rooming houses and private hotels included were those with rates affordable for people on pensions; the great majority of rooming houses in St. Kilda are in this price range. They were located from local government lists, the personal knowledge of social workers, and community nurses. Special accommodation houses are state-registered premises established originally for the elderly disabled but catering also to the physically and mentally handicapped in general. They provide full board and supervision. They operate on a commercial basis with no subsidies, and in most cases the invalid's or elderly person's pension is the price for this accommodation.

We estimated the size of the study population and its distribution among the three types of accommodation, or three strata, after preliminary fieldwork in the area. We aimed to sample each of the three strata over as short a time as possible to approximate a point prevalence.

In each of the shelters, we used the bed numbers on an overnight census list to select a one-in-two random sample, stratified by sex, of all occupants known or thought to be eligible on the basis of age. The total size of the shelter subsample was 222. We did not attempt to replace those who refused to participate, had left, or could not be located after a number of return visits. A replacement was made when a subject was found to be over 60 years old or in the occasional case of an individual who had already been included in sampling at another site. In the early stages of the study, as a reflection of the unfamiliar and difficult conditions, the raters interviewed 36 men residing in the shelters who were not part of the random sample. We included the results of these interviews in the analyses after checking that the age and diagnostic profiles for this group did not differ significantly from those of the remainder of the group in the shelters.

The managers of all 25 special accommodation houses operating in the area were approached, and 24 agreed to participate. A one-in-two sample of all occupants less than 61 years of age was selected randomly from room or bed numbers in each house. That subsample size was 85.

The caretakers or owners of all 83 low-cost rooming houses and private hotels identified and operating in the area were approached, and 47 agreed to participate in the survey; there were no apparent differences in type or size of facility between those who participated and those who did not. In each participating house a one-in-three sample of all occupants known or thought to be eligible on the basis of age was selected randomly from room numbers. The subsample size was 217. When necessary, several return visits were made to locate the residents.

Each respondent received $5 as recompense for time taken and inconvenience. Respondents were asked to give informed verbal consent to the interview, and the information was used confidentially.

Sample Characteristics

Two-thirds of the individuals sampled (346 of 524) were located and interviewed. The proportion varied by type of accommodation: 64% in the shelters, 93% in the special accommodation houses, and 57% in the rooming houses and private hotels. Data from interviews with the 346 randomly selected respondents and from the additional 36 men interviewed in the shelters are included in the analyses.

Of the 382 subjects interviewed, 69 were female and 313 were male. Of the male subjects, 8% were aged 15 to 24 years, 22% were 25 to 34 years old, 29% were 35 to 44, 23% were 45 to 54, and 19% were 55 to 60. Approximately half (48%) of the female subjects were between the ages of 35 and 54 years, and 28% were below that age. Age and sex data were obtained on two-thirds of the group sampled but not interviewed. The age and sex profile of this group (141 men, 34 women, three of unknown sex) was similar to that of the group interviewed.

Twenty-eight percent of the respondents (107 people) were born outside Australia, and 58% of these were born in countries with national languages other than English. In comparison, the percentage of the general population born outside Australia is 40% for the total population of inner Melbourne and 30% for Melbourne (19). Two people were excluded from the study before interview because of an inadequate command of English.

Of the 382 respondents, 355 reported living for at least the previous month in one or more of the accommodation types surveyed. That is, over 90% of those we interviewed had been homeless or disaffiliated for at least 1 month. This represents chronic homelessness according to Vergare and Arce (4) (or chronic disaffiliation by analogy). Thirty people (28 men and two women), or 8% of those interviewed, said they sometimes or often slept "rough," that is, without shelter of any kind. For the men interviewed in the shelters, this percentage was higher (12%).

Over half (59%) of those interviewed were receiving invalid pensions or sickness benefits. Most of the remainder were receiving other pensions or benefits. Twenty-nine people (8%) reported current paid employment, which was full-time for 22 (6%).

TABLE 1. Major *DSM-III-R* Diagnoses Among 382 Homeless or Disaffiliated People in Inner Melbourne

	Lifetime		Current	
Disorder	N	%	N	%
Mood disorders	96	25	46	12
Bipolar disorder	13	3	4	1
Major depression	78	20	25	7
Dysthymia	0	0	15	4
Depressive disorder not otherwise specified	5	1	2	1
Psychotic disorders	82	21	67	18
Schizophrenia	51	13	44	12
Schizophreniform disorder	0	0	0	0
Schizoaffective disorder	6	2	6	2
Delusional disorder	4	1	2	1
Brief reactive psychosis	0	0	0	0
Psychotic disorder not otherwise specified	21	5	15	4
Substance-related disorders	189	49	99	26
Alcohol abuse	14	4	0	0
Alcohol dependence	162	42	85	22
Other substance abuse	14[a]	4	6	2
Other substance dependence	63[b]	16	30	8

[a] Sedative, N=1; cannabis, N=9; stimulant, N=1; opioid, N=0; cocaine, N=1; hallucinogen, N=1; other, N=1.

[b] Sedative, N=11; cannabis, N=14; stimulant, N=9; opioid, N=3; cocaine, N=1; hallucinogen, N=3; other, N=4; poly drug, N=18.

RESULTS

Alcohol dependence, dependence on other substances, schizophrenia, and major depression were the most prevalent disorders (table 1). Approximately 20% of the respondents received diagnoses of psychotic disorders; the rates for current (past month) and lifetime diagnoses of psychotic disorders differed only slightly. For the broad diagnostic categories of mood and substance-related disorders the rate of current diagnosis was about half the lifetime rate.

To the mood disorder category we assigned the subjects with major affective disorders, including major depression and bipolar disorder, and dysthymia (the latter occurred in only 4% of the respondents). The psychotic disorders category includes all other psychotic diagnoses (table 1).

Almost half the people interviewed each received at least one diagnosis of severe mental disorder for the month before the interview, and over 70% received lifetime diagnoses (table 2). One in three of the female subjects was diagnosed as currently psychotic. For the male subjects the proportion with current substance abuse or dependence was 29%. Nineteen percent of those with current diagnoses (9% of the respondents) and 29% of those with lifetime diagnoses (21% of the respondents) each received diagnoses in more than one

TABLE 2. Categories of *DSM-III-R* Disorders in Male and Female Homeless or Disaffiliated People in Inner Melbourne

Disorder Category (mutually exclusive)	Lifetime[a]						Current[a]					
	Male (N=313)		Female (N=69)		Total (N=382)		Male (N=313)		Female (N=69)		Total (N=382)	
	N	%	N	%	N	%	N	%	N	%	N	%
One category												
Mood disorders	29	9	2	3	31	8	22	7	3	4	25	7
Psychotic disorders	26	8	24	35	50	13	30	10	22	32	52	14
Substance use disorders	104	33	10	15	114	30	63	20	4	6	67	18
Two categories												
Mood and substance	42	13	6	9	48	13	17	5	2	3	19	5
Mood and psychotic	5	2	0	0	5	1	2	1	0	0	2	1
Psychotic and substance	12	4	3	4	15	4	11	4	2	3	13	3
All three categories	11	4	1	1	12	3	0	0	0	0	0	0
No disorders	84	27	23	33	107	28	168	54	36	52	204	53

[a] Lifetime diagnoses include current diagnoses (except dysthymia), but an individual with a current diagnosis in one category may have lifetime diagnoses in one or two other categories.

TABLE 3. Categories of *DSM-III-R* Disorders in Occupants of Shelters, Special Accommodation Houses, and Rooming Houses and Private Hotels in Inner Melbourne

Disorder Category (mutually exclusive)	Lifetime[a]						Current[a]					
	Shelters (N=179)		Special Accommodation Houses (N=79)		Rooming Houses and Private Hotels (N=124)		Shelters (N=179)		Special Accommodation Houses (N=79)		Rooming Houses and Private Hotels (N=124)	
	N	%	N	%	N	%	N	%	N	%	N	%
One category												
Mood disorders	14	8	3	0	14	11	11	6	6	8	8	7
Psychotic disorders	14	8	24	30	12	10	15	8	23	29	14	11
Substance use disorders	65	36	18	23	31	25	45	25	3	4	19	15
Two categories												
Mood and substance	30	17	0	0	18	15	10	6	0	0	9	7
Mood and psychotic	0	0	1	1	4	3	1	0	1	1	0	2
Psychotic and substance	11	6	1	1	3	2	10	6	1	1	2	1
All three categories	8	5	3	4	1	1	0	0	0	1	0	0
No disorders	37	21	29	37	41	33	87	49	45	57	72	57

[a] Lifetime diagnoses include current diagnoses (except dysthymia), but an individual with a current diagnosis in one category may have lifetime diagnoses in one or two other categories.

broad diagnostic category. The overlap between substance abuse or dependence and the other disorders was especially notable.

The pattern of disorders varied among the three accommodation types (table 3). Substance-related disorders and comorbidity were most prevalent in the shelters, where 36% of the respondents were diagnosed as having current (past month) substance-related disorder, alone or in combination. The pattern in the rooming houses and private hotels was similar. The highest prevalence of current psychotic disorders was found in the special accommodation houses (32%).

Summary indicators of past psychiatric treatment were derived from information in the SCID-R overview and other parts of the interview. We defined psychiatric treatment as hospitalization in a psychiatric or drug and alcohol treatment facility and/or contact with a mental health or general medical professional for "emotional problems." Of the subjects who did not receive lifetime diagnoses, 18% reported past psychiatric treatment. Most of those with lifetime diagnoses of psychotic disorders reported treatment (91%) and hospitalization (83%) at some time. Those with mood and substance-related disorders reported lower rates for previous psychiatric treatment (63% and 59%, respectively) and hospitalization (43% and 40%). The overall rates for hospitalization and treatment in the respondents were 40% and 56%, respectively.

On the basis of the 38 retest interviews, kappa coefficients (20) were calculated for the broad diagnostic categories and for the major diagnoses. The kappas for current and lifetime diagnoses in the broad diagnostic categories ranged from 0.54 to 0.95, and for any disorder they were 0.95 and 0.77, respectively (with mean base rates of 78% and 55%). The kappas for current and lifetime diagnoses of schizophrenia were both 0.88 (mean base rate, 32%), for alcohol dependence they were 0.85 and 0.89 (mean base rates, 24% and 42%), and for lifetime diagnosis of major depression the kappa was 0.54 (mean base rate, 13%). (For current diagnosis of major depression the mean base rate was less than 5% for the test-retest subsample.) The results suggest a high level of diagnostic agreement for the psychotic and substance-related disorders. For mood disorders the agreement was lower but still relatively good.

Informal consensus diagnoses of both current and lifetime organic mental disorder, mostly unspecified in the absence of formal clinical evaluation, were made for 26% of the respondents. There was considerable overlap with the severe (functional) mental disorders, but 48 people (13% of the respondents) were assigned current diagnoses of organic disorder alone, and 30 people (8%) were given lifetime diagnoses of organic disorder alone. These estimates would increase the prevalence of severe mental disorder in the sample to 59% for current disorder and 80% for lifetime disorder.

DISCUSSION

We trained and supervised clinician interviewers in the use of a standardized diagnostic instrument, a procedure unusual in other studies of this type (2, 3), to diagnose severe functional mental disorders in representative groups of homeless and disaffiliated people in inner Melbourne. By less precise means we gained some indication of the prevalence of organic mental disorders.

The interview rate of 66% is probably acceptable in the setting. We cannot be sure, however, what selection biases may have been introduced, even though the age distribution was not obviously skewed.

We restricted the survey to clearly defined severe mental disorders. Many people living in these places are likely to be distressed in a significant, yet nonspecific way, irrespective of the presence of severe mental disorder. In addition, we did not attempt to diagnose the severe personality disorders, which are very disabling but difficult, and perhaps impossible, to diagnose in cross-section from the subject's report alone.

The reliability of the SCID-R in this survey appears good for the broad diagnostic categories and for the individual diagnoses on which it could be tested in the reliability subsample. In general, the interviewers rapidly became skilled and efficient in the use of the instrument. Instruments such as the SCID-R tend to underestimate lifetime disorder (21). This fits with our impressions from supervising the interviews and may be suggested by the patterns of service use reported here, although these may equally reflect treatment for other disorders.

The variation in pattern of disorder by type of accommodation is also congruent with expectations. Many residents of special accommodation houses, for instance, moved there directly from psychiatric hospitals, and residents of these facilities have almost no access to alcohol or illicit drugs.

There was a strikingly high rate of severe mental disorders in the population surveyed here, as compared, for example, with population rates from the American Epidemiological Catchment Area Study (22). Even so, this survey did not address the major issues of physical illness or disability (23–25) or mental retardation in the overall group or dementia in the elderly.

The high rates of mental disorder and the rates for individual diagnoses, such as schizophrenia, found in this survey are consistent with rates suggested by overseas and local surveys of homeless people (2–6, 15). The recent Los Angeles study employing the Diagnostic Interview Schedule (3) provides a particularly useful comparison. Similar rates of disorder were found, although our clinical interviewers used the SCID-R to make diagnoses according to the *DSM-III-R* hierarchical rule. The overall rate of past hospitalization for psychiatric and substance abuse disorders was also close to that described by Gelberg et al. in Los Angeles (13).

Individuals who are marginally accommodated in Melbourne appear to have mental disorders in proportions similar to those among truly homeless people. This similarity was suggested by the comparable patterns of disorder found in occupants of the shelters and rooming houses in our study.

It appears that disaffiliated people with severe mental disorders are less likely to live on the streets in Melbourne, where low-cost accommodation is more readily available, than in many U.S. cities. The miserable conditions under which these people live are nonetheless "symptomatic of the (relative) lack of a comprehensive system of care for the long-term mentally ill" (26). At the same time, neither those with severe mental disorders nor homeless people are a homogeneous population, and individuals in these groups have diverse needs and outlooks (13, 26, 27).

A critical issue is how people with severe mental disorders become disaffiliated and homeless. We have considered concurrent and sequential comorbidity and noted, as did Koegel et al. (3), the major overlap between substance-related disorders and the mood and psychotic disorders. This may well be an important factor. Other authors (13, 24, 28) have commented recently on the multiple problems and disabilities—social, mental health, physical, and criminal—commonly experienced by homeless people and have speculated on the role of such multiple factors in the genesis of homelessness (24, 28). Yet others have noted that for some people disaffiliation or homelessness appears to be the most recent stage in a lifelong or long-term series of problems, or a "drift down," and not the result of a unique crisis (29). It is likely that a variety of factors contribute, including childhood experiences (30), premorbid socio-economic status, intelligence, education, social support, personality, and the prevailing economic and social policy climates (31).

The high rates of disorder indicated by this survey provide one guide to service provision and a baseline against which service changes can be evaluated. It is important, though, to avoid uncritical use of such data in planning services for the severely mentally ill. Even if the high rate of severe mental disorder in homeless and disaffiliated peoples were shown to be simply a result of reduction in numbers of hospital beds for the chronically mentally ill, the appropriate response would not necessarily be a re-expansion of this kind of facility. The problem may be seen as a low-level, steady growth of the population of chronically ill, handicapped individuals (32), who form a minority of those who develop severe mental disorders (32–34). The most helpful response is likely to be flexible (26), providing a range of services—preventive, restorative, and supportive—in a variety of hospital and community settings.

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Media Power and Public Mental Health Policy

Luis R. Marcos, M.D., M.Sc.D.

The author describes the functions of the news media and their influence on public mental health policy making. News media functions are divided into the categories of selecting the news, reporting information, serving as a channel of communication, presenting views and opinions, and legitimizing the issues. These functions are illustrated by focusing on a highly publicized New York City policy to involuntarily hospitalize mentally ill homeless people living in the streets. Strategies are suggested to mental health professionals on how to effectively interact with the news media.

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In the United States today, few people have to be convinced of the power of the media in influencing public opinion and social change. Indeed, the media shape attitudes, sell political candidates, and interact with the public constantly. The power of the media, particularly the news media, has been concentrated in newspapers, radio, and television. These news media have a decisive impact on the formulation and legitimization of public policy. Simply being discredited by the news media is often enough to taint public officials and delegitimize public policies, no matter how solidly planned or socially valuable (1).

Policy making is a dynamic process that requires interaction and play of power among different advocate and interest groups; the executive, legislative, and judicial branches of government; public bureaucracies; and the news media. Because psychiatry often deals with serious social problems that are substantially affected by public policies, it is essential that mental health professionals, particularly those in administrative and policy-making positions, understand the dynamics of policy making, including the role of the news media, in order to more effectively influence government decision-making processes that constantly shape the way mental health care is organized (2). Although the topic of media power and influence has been studied by sociologists, to my knowledge, the psychiatric literature has given limited attention to this subject.

The purpose of this paper is to describe the functions of the news media and their influence on public mental health policy making, illustrate these functions by focusing on a highly publicized New York City policy to involuntarily hospitalize seriously mentally ill homeless individuals living in the streets, and suggest some strategies for mental health administrators and policy makers on how to effectively interact with the news media.

THE POLICY

On October 28, 1987, the mayor of the City of New York instituted a new public policy to involuntarily remove from the streets severely mentally ill homeless individuals who were neglecting their essential needs for food, clothing, shelter, and medical care and who, by reason of their mental illness, lacked the capacity to comprehend the need to protect themselves from obvious danger and were at risk of physical harm within the reasonably foreseeable future (3). Once identified and evaluated by the psychiatrist in an interdisciplinary mobile crisis unit called Project Help, these patients were transported to Bellevue Hospital's psychiatric emergency room for further evaluation and, if indicated, admission to a newly created intensive-care psychiatric inpatient unit. After the acute phase of hospital care, the patients had access to a variety of ambulatory and institutional aftercare programs specifi-

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cally developed for this initiative. Legal representation was available to these patients in accordance with the rights of all psychiatric patients in New York State (4).

This policy is particularly useful in illustrating the influence of the news media on the formulation of public mental health policy because of the extensive local and national coverage that it received. In the process, advocate and interest groups, political leaders, and the mental health establishment closely interacted with the media and often articulated strong opinions for and against the new policy.

FUNCTIONS OF THE NEWS MEDIA

Selecting the News

Obviously, not all events that occur in one day make the news. The usual criterion for selecting news out of the dross of everyday events is public interest. Other generally accepted criteria for the selection of news include the unusual and unexpected nature of the event. In addition, an event will be more readily selected as newsworthy if it is consonant with the interests and image of a particular news organization, reporter, or editor. In this regard, the media play a censorship role, and what is concealed may constitute news. Furthermore, for planning and pragmatic reasons, news media must set a limit to the length of a story and maintain a balance between different types of news (e.g., local, international, sports) regardless of the real occurrences in the world of events. Thus, administrative factors affect both the selection of news and how the events are presented to the public (5).

From a public interest perspective, the new policy was the first government effort to involuntarily remove from the streets and hospitalize homeless mentally ill individuals who, due to neglect of their essential needs, were considered a danger to themselves in the reasonably foreseeable future. Previously, police intervention was considered only when behavior indicative of dangerousness to self was actively displayed by the individual and the risk of death was deemed substantial or imminent. The new policy was unexpected in that it was quietly planned and implemented in only 5 months. It was also controversial, particularly because its less strict criteria for involuntary transportation and hospitalization, although supported by case law, were not explicitly included in the New York State Mental Hygiene Law. Thus, the new policy highlighted the perennial debate between the value of protecting disabled citizens and letting people decide their own destiny no matter how dangerous their choices might be.

Reporting Information

The most apparent function of the media is to provide information to the public. Concerning the city's new policy, characteristic of many news reports were the detailed accounts of the patients, their life histories, and clinical conditions. Reporters wanted detailed information in order to add depth and credibility to their stories, and city officials felt that given the questions raised about the merits of the new policy, the initiative could gain public support through examples of how real people in real need of help were being cared for.

Conversely, interest groups that opposed the new policy also needed to back up their positions with concrete examples of how the policy was negatively affecting people's lives. The best example was the case of Joyce Brown, also known as Billie Boggs, who was the first homeless individual picked up by Project Help. With the support of American Civil Liberties Union lawyers, she waived her right to confidentiality in order to show publicly that her civil liberties had been violated, since she did not consider herself either sufficiently mentally ill or sufficiently dangerous to herself to have warranted her involuntary removal from the street and commitment to Bellevue Hospital (6–8; "NBC Nightly News," Nov. 2, 1987).

In addition to providing information, the news media decide how to portray the events. In the process of editorializing, they often simplify or sensationalize the events through the presentation of stereotypes. The press coverage of Billie Boggs illustrates how the news media can simplify complex issues into what they perceive as more marketable stories. By focusing so much on this case at the expense of the overall initiative, the media portrayed a one-dimensional view of the new policy. To dramatize the case, newspapers used headlines such as "Woman Swept Up Is Fed Up" (9), "Street Survivor Fights" (10), "Please Commit Billie Boggs" (11), "I'm a Political Guinea Pig" (12), and "The 'Victory' of Billie Boggs" (13). In addition, in the days after the new policy was implemented, some local newspapers carried sensationalistic reports on the initiative with provocative headlines such as "Street People Sweep Starts" (14), "Corralling the Homeless" (15), and "A Good Night's Sweep" (16).

Serving as a Channel of Communication

Another function of the news media is to serve as a public means of communication, which can be used to exert pressure on the different actors and constituencies involved in a new policy. In the case of the new policy in New York, a good illustration was the dialogue between city and state officials through the newspapers. For instance, shortly after the announcement of the new policy, local newspapers reported that the mental health care resources in the city might not be enough for the success of the initiative and that the state needed to provide additional resources (17). Subsequently, using the media as a way to pressure the state, city officials charged that the state psychiatric centers were not accepting enough patients in need of long-term care and that this situation would have a negative impact on the success of the new policy (18).

State officials responded, also through the media, that the new policy was like a return to the dark days of institutionalization (19). In turn, city officials' pressure on the state increased (20), and in one editorial entitled "Albany Betrays the Street People" (21), the *New York Post* said in part, "The Mayor launched a bold initiative some weeks back to rescue the most desperate of the mentally ill street people. That effort, sad to say, seems to be going nowhere. It is being blocked, willfully, by an obdurate bureaucracy in Albany." Finally, 2 weeks before the new policy was scheduled to begin, the state announced its willingness to join the city by providing 50 beds in a state psychiatric center for those homeless patients in need of long-term care. The next day, the press clearly linked that support to the newspaper-mediated pressures exerted by the city on the state during the prior weeks (22).

Presenting Views and Opinions

The news media frequently provide a public platform for the discussion of the divergent opinions held by interest groups and government officials. Although there was widespread public support of the city's new policy and the media reflected this positive sentiment (23, 24), there were critics who denounced the initiative on different fronts. For example, the Coalition for the Homeless, an advocacy group, contended that the initiative was simply a political statement, a publicity stunt on the part of the mayor, since there were insufficient psychiatric beds in the city and state hospitals to house existing patients (25). Other critics maintained that the initiative was a "drop in the bucket" or a smoke screen to hide the overwhelming problems with the growing number of homeless individuals, the poor conditions of the city shelters, and the lack of affordable housing in the city (26; ABC News, "Nightline," Nov. 27, 1987). There were also those who dismissed the initiative as a desperate attempt to clean the streets of fashionable neighborhoods of unsightly and disturbing people (27).

Civil libertarians, and particularly the American Civil Liberties Union, were the most consistently outspoken group against the initiative. The American Civil Liberties Union saw the new policy for involuntarily removing the homeless mentally ill as a danger to the individual's civil liberties. It also considered the new policy illegal and unconstitutional, since the state law did not include either neglect of essential needs or dangerousness in the foreseeable future as part of the civil commitment criteria (28). City psychiatrists were attacked by civil libertarians for becoming puppets of the government, and the initiative was equated with psychiatry in Russia (29).

The media also communicated the position of mental health experts. For example, John A. Talbott, M.D., Past President of APA, was quoted as saying, "Koch is the first government official who has truly acknowledged the massive mistakes made by deinstitutionalization" (30). Similarly, after the mayor presented the new policy at the American Psychological Association's annual meeting, the media reported the members' support (31). In addition, the Alliance for the Mentally Ill, an association of families and friends of the mentally ill, saw the mayor's initiative as "blowing the whistle on a situation that for years had been steadily worsening" (32). On the other hand, the press reported that some mentally ill homeless, fearful of being taken to the hospital against their will, appeared to be avoiding the streets by spending more time in the subways (33).

The news media often express their own opinions through editorials. In the process, they influence the public and become opinion shapers. Concerning the initiative, the media portrayed the mayor of the city as courageous and sensitive to the needs of the mentally ill and expressed the view that the new policy was a positive and humane initiative (34–37). However, the media also emphasized that the mayor would have to be held personally responsible for the success or failure of the policy (38).

Legitimizing the Issues

Perhaps the most critical function that the news media play is to serve as a legitimizing power (39). Indeed, the media influence and validate a policy in the public's eye not only through editorials but also through the manner in which the events are selected, organized, and presented. They also exert influence by focusing on particular positions or by emphasizing certain positive or negative aspects of a policy. This legitimization function is also achieved by shaping the opinions of people, especially those who have not made up their minds.

As a legitimizing power, therefore, the media determine what information is relevant for the public, create and use experts on the subject through the development of media personalities, and legitimize or condemn policies through the application of media-based criteria. In the case of New York City, the validation of the mayor's initiative by the news media was evident in the almost daily positive portrayal of the new policy.

The news media also validated the new policy by focusing on its symbolic impact and offering a positive perception of the actions taken by the city to address the problem. Even when the city's initiative did not succeed in substantially reducing the number of homeless mentally ill people living in the streets, the media recognized the effort of public officials because it showed that they cared for these people and that they were willing to do something about the problem (40, 41). In this regard, the news media know that public opinion sometimes judges a public policy more in terms of its good intentions than its tangible accomplishments (42).

RECOMMENDATIONS

Obviously, what is presented through the news media matters and has consequences. Therefore, mental health professionals in policy-making and administrative positions need to familiarize themselves with the different functions of the news media and their influence on mental health policies. Although skillful interaction with the media may not be sufficient for the success of a bad public policy, it is an important factor in gaining public support for new policies or program initiatives, particularly those which are considered controversial.

First, it is important to recognize in advance those policies which have the potential for being newsworthy. Once they are identified, there is a need for planning on how to present the issues to the press. Press briefings before the implementation of new policies are useful, but they should be well structured and consistent with patient confidentiality guidelines, particularly if the issues involve patient care.

Second, information regarding the specifics of how well or how poorly the policy is working should be provided to reporters as soon as the spokespersons are ready to give it and not before. Then, they should supply information until all the points in support of the policy are made and the reporters are satisfied. It is important to be forthcoming and willing to discuss all issues and to give the impression that there is nothing to hide, including the expected problems and limitations of the new policy. When spokespersons interact with reporters, it is important to distinguish information provided on the record, off the record, or as background. Comments should be given on the record when the spokesperson wants and expects to be quoted extensively and by name. Information should be provided off the record or as background only when the spokesperson needs to give the reporter guidance on the issues but is constrained from doing so officially because of the organization's media relation practices. Such a risk, however, should be taken only when the reporter is considered trustworthy.

Third, once the policy is implemented and receives media coverage, there must be a willingness to follow up. If certain things go wrong, the use of damage control techniques is important. For instance, it is almost always better to be available and talk about the problems than to be unavailable or unreachable for comment. At the same time, it is preferable to select the means of communicating bad news. In this regard, it is always useful to interact with news media that are particularly interested in the substance of the policy and with reporters with whom a relationship of mutual respect has been established.

To enhance the possibility of a successful interaction with the news media, the availability of experts skilled in the techniques of how to present issues and events to fit media logic and procedures has become increasingly important in mental health organizations. Although this resource can be particularly useful in organizations with extensive public exposure, it is important to carefully select these spokespersons and provide them with training specific to the mental health field.

While more research is needed to better understand the role of the news media in mental health policy making, the public performance of mental health administrators and policy makers needs to be increasingly media-conscious. This is because public policies or program initiatives that are not supported by the news media are often doomed to failure, and the administrators and policy makers involved are themselves likely to become objects of public allegations and attack.

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Antidepressant Effects of Right Versus Left Unilateral ECT and the Lateralization Theory of ECT Action

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In a random-assignment, double-blind, controlled comparison of right versus left unilateral ECT in 30 melancholic men, the two methods were not significantly different in overall antidepressant potency, although there was a significantly faster rate of improvement with left unilateral ECT. These results imply that the antidepressant effects of ECT cannot be attributed primarily to right hemisphere mechanisms, as others have postulated.

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A putative therapeutic advantage of right versus left unilateral ECT in the treatment of melancholia has been invoked to support a postulated right hemisphere mechanism for the antidepressant effects of ECT and a general theory of cerebral hemispheric asymmetry in depression (1–4). Of the studies variously cited in support of this right unilateral advantage, only five employed a double-blind, controlled method (5–9); of these, only two (6, 9) found a statistically significant therapeutic advantage for right versus left unilateral ECT.

One of us recently reported a striking instance of recovery from melancholia in a fully dextral man after six left unilateral ECTs (10), an event that suggested that it was premature to attribute the beneficial effects of ECT in melancholia primarily to right hemisphere mechanisms. We now report the results of a random-assignment, double-blind, controlled comparison of right and left unilateral ECT in melancholic men, demonstrating that left unilateral ECT is not less effective in treating melancholia than right unilateral ECT.

METHOD

The study was conducted on the inpatient academic psychiatric service of a large Veterans Administration Medical Center. Selected were all consecutive male patients referred for ECT who satisfied *DSM-III* criteria for major depression, melancholic subtype (but with duration of illness over 4 weeks), who had not received ECT within the prior 6 months and who received a baseline rating of at least 15 on a modified, 15-item version of the Hamilton Rating Scale for Depression (11).

This study developed in the context of an ongoing comparison of bilateral and right unilateral ECT. After 13 patients had been randomly assigned to these two conditions (seven to right unilateral ECT and six to bilateral ECT), a left unilateral ECT condition was added to the random assignment schedule and 34 more patients were included. Thirty patients were included in the present study; they ranged in age from 34 to 68 years (mean=58.7 years). Nineteen patients received right unilateral ECT, and 11 received left unilateral ECT. All patients gave written informed consent.

Patients were rated on the Hamilton depression scale before treatment and within 24 hours after the third and the sixth ECTs by one of the authors (R.A. or C.V.), who was unaware of treatment electrode placement. The intraclass correlation coefficient (equivalent to weighted kappa) between the two raters for 24 randomly selected joint Hamilton scale ratings was 0.99. Patients who received more than six ECTs were switched to alternative treatment electrode placements

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Bulbul Bahuguna, M.D., assisted in data collection.

as part of another study, and no further Hamilton rating scale scores were obtained.

Hand preference was assessed by inquiring about the hand used to hammer a nail, scissor paper, throw a ball, and flip a coin; by observing the patient write his name on a line; and by asking whether hand preference had ever changed. Patients were classified as dextral only if they had always used the right hand for all tasks and wrote with the hand below the line. Assignment to treatment electrode placement was done without consideration of handedness.

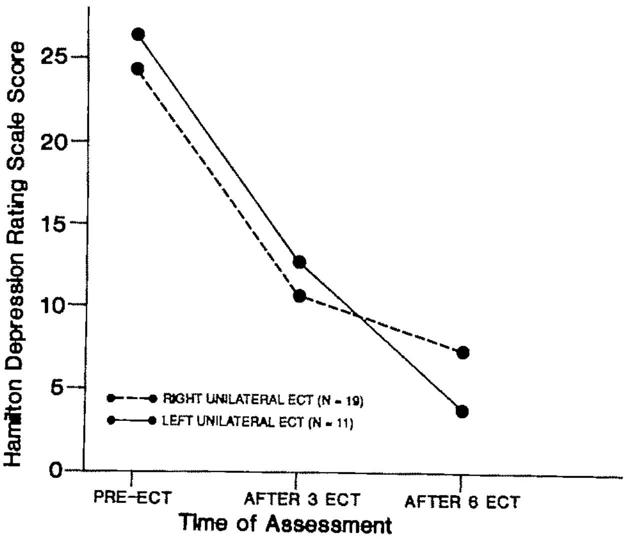
After glycopyrrolate-methohexital-succinylcholine anesthesia, ECT was administered with a Somatics Thymatron brief-pulse instrument set to deliver a charge of 378 millicoulombs in each instance (0.9 A, 1 msec pulse width, 140 pulses/second for 3 seconds). All treatments were administered with the d'Elia placement (12). Motor seizure duration was monitored with the cuffed-limb method (13), and EEGs were recorded with a single-channel chart recorder. At the stimulus dose applied, no seizures shorter than 25 seconds occurred, and no repeat stimuli were given. During the study, all psychotropic medications were withheld except for short-acting benzodiazepines for nighttime sedation.

A repeated measures analysis of variance (ANOVA) (two-factor mixed design with repeated measures on one factor) was used to analyze the data, with appropriate post hoc comparisons according to Scheffé.

RESULTS

Figure 1 illustrates the Hamilton scale scores for the two groups at baseline and after the third and sixth ECTs. Inspection of the figure reveals approximately equivalent antidepressant effects for the two methods after three ECTs, with a leveling off of this effect after six ECTs for right, but not left, unilateral ECT. Six right unilateral ECTs reduced Hamilton depression scale scores by 70%, compared with 85% for six left unilateral ECTs. ANOVA revealed a significant treatment main effect, with ECT demonstrating great overall effectiveness in reducing depression scores ($F=117.50$, $df=2, 57$, $p=0.000001$). There was no significant main effect of treatment electrode placement ($F=0.005$, $df=1, 28$, $p=0.95$); right and left unilateral ECT were not significantly different overall in reducing depression scores. Finally, there was a significant interaction between treatment electrode placement and assessment time ($F=4.95$, $df=1, 57$, $p=0.03$); post hoc comparisons showed a significant fall in depression ratings from the third to the sixth ECTs for left unilateral ECT ($F=3.70$, $df=2, 27$, $p=0.04$) but not for right unilateral ECT ($F=0.84$, $df=2, 27$, $p=0.4$). Mean±SD motor seizure durations for the 36 seizures received per patient did not significantly differ between the two groups: 47.8±10.5 seconds versus 44.2±12.0 seconds for right unilateral and left unilateral ECT, respectively ($t=0.86$, $df=28$, $p=0.40$).

FIGURE 1. Hamilton Rating Scale for Depression Scores for 30 Men Before ECT and After Right Unilateral and Left Unilateral ECT



Only one patient was not fully dextral—he was born left-handed and was forced to use his right hand for academic work in school but still threw a ball with his left hand. He exhibited 78% improvement after left unilateral ECT. Excluding him from the data analyses did not significantly change the probabilities obtained.

Two patients were incidentally readmitted for second courses of ECT more than 6 months after the end of their initial participation in the study. They were again included in the random assignment schedule but not in the figure or data analyses. One patient received his first treatment course with right unilateral ECT and his second with left unilateral ECT, improving 97% and 96%, respectively. The other patient received left unilateral ECT the first time, with a 64% improvement, and right unilateral ECT the second time, with a 27% improvement.

DISCUSSION

Our results demonstrate that although right and left unilateral ECT were not significantly different in overall antidepressant potency, improvement was faster with left unilateral ECT, primarily from the third to the sixth ECTs. A possible therapeutic advantage for left over right unilateral ECT is consistent with the recent report (14) of an association between ECT-induced lateralized EEG slowing and treatment response to right unilateral and bilateral ECT. In that study, right-sided EEG slowing was associated with right unilateral ECT and with a smaller therapeutic response, and left-sided EEG slowing was associated with bilateral ECT and with a greater therapeutic response. Like bilateral ECT, left unilateral ECT has been associated with EEG slowing that is accentuated over the left hemisphere (15, 16); thus, left unilateral ECT might be expected to have a therapeutic profile more closely resembling that of bilateral rather than right unilateral ECT.

Might the limitation to six ECTs have affected the observed efficacy of right and left unilateral ECT because of the different speeds of response to the two methods? This seems unlikely, since the median improvement after six ECTs was 84.5% for the entire sample, a figure demonstrating the generally excellent effect achieved by the fixed course of six ECTs. Moreover, the figure shows an apparent therapeutic advantage of left unilateral ECT that developed along the treatment course, suggesting that it might increase further with additional treatments.

If the substantial electrical charge we employed had overwhelmed all tendencies to focal onset and lateralized distribution of seizures—such as presumably occur with marginally suprathreshold stimuli—there would have been no expression of lateralized hemispheric effects. But lateralized effects were found, albeit in a direction opposite to that previously claimed, and we find no reason to attribute our results to the dose of electrical charge.

Differences in stimulus administration technique may account for the differences in clinical results between the present study and the earlier ones reported. We used a brief-pulse stimulus administered with the wide temporoparietal d'Elia placement (12). In contrast, all but one (7) of the earlier studies used a sine wave stimulus, and none used a wide temporoparietal electrode placement; therefore, all used methods that were less efficient than their modern counterparts.

Our observations are consistent with a majority of the methodologically adequate comparisons of the antidepressant effects of right versus left unilateral ECT (5–9) and do not support the hypothesis that the antidepressant action of ECT is produced through mechanisms lateralized to the right cerebral hemisphere. Indeed, if the observed trend toward a therapeutic advantage for left versus right unilateral ECT is verified with further study, only quite different mechanisms can explain this advantage, and the general theory of cerebral hemispheric lateralization of depression (17) must be reconciled to it.

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Birth Order of Patients With *DSM-III-R* Somatization Disorder

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A sample of 143 patients, 76 meeting strict DSM-III-R *criteria for somatization disorder and 67 somatizers, was studied using Slater's index to measure birth order position. The results showed that birth order position was not associated with the diagnosis of somatization disorder and that sibship position in both groups occurred by chance. Thus, although environmental factors may influence the development of somatization disorder, the expression of environmental influence through birth order is unlikely.*

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The *DSM-III-R* diagnostic criteria for somatization disorder evolved from the *DSM-III* criteria as a shortened version of the Feighner criteria for Briquet's syndrome (hysteria) (1–5). Although the diagnostic tools for somatization disorder are reliable, etiological factors in the disorder remain unclear. It has been postulated that the disorder is caused by environmental factors (6–9), and by studying birth order, useful information about potential environmental influences may be obtained. If somatization disorder is determined solely by an abnormal gene, all siblings should have the same probability of having the disorder, and somatization disorder should develop in a normal distribution among birth order positions. An abnormal distribution of the disorder among the birth order positions would suggest strong environmental influences in the etiology of the disorder.

A number of studies have found the firstborn position to be prominent in various hysteria-related conditions. Ziegler et al. (8), in a study of 100 patients with a diagnosis of conversion reaction, found a significantly higher percentage of patients in the firstborn position. This study did not have a control group, nor did it follow strict research criteria for selection of subjects; that is, it used reasons for consultation and the predominant clinical findings based on *DSM-I*. The study's incomplete sibships (the youngest subject's age was 14) also introduced potential distortion (10). Stephens and Kamp (9), in a study of 100 patients with hysterialike disorders, found that 30% of the patients studied were firstborn or only children. This study used a wide range of diagnoses (including dissociative disorders) and different cohort samples without control groups (10–12). Morrison (6) studied patients meeting the *DSM-III* criteria for somatization disorder and a control group from his clinical practice to show significantly earlier birth order positions for women with somatization disorder (Slater's index=0.3678±0.0415).

However, other studies have shown a normally distributed birth order. Ljungberg (13), in a study of 380 "hysterical persons," found no difference in sibling position. Roy (14), in a study of 31 patients meeting the *ICD-8* criteria for hysterical neurosis and 31 with depressive neurosis, found no significant difference in sibling position between patients in the two groups. A study by Tsuang (15) showed that birth order position was not significant (Slater's index=0.5430±0.0737) for 34 women meeting the *ICD-7* criteria for hysteria. Wilson-Barnett and Trimble (16), using patients with a clinical diagnosis of hysteria and two control groups, did not find differences in birth order. Since studies have shown early, middle, and late birth order positions and have used subjects with multiple hysterialike disorders, the question of birth order (and thus, of environmental impact) in somatization disorder remains unclear. This paper reports the findings on birth order for patients meeting strict *DSM-III-R* criteria for somatization disorder and for patients with fewer than the required number of symptoms (somatizers).

METHOD

This study was performed as part of a larger study comparing the cost effectiveness of treatments and the functional health status of patients from a primary care population. Informed consent was obtained from all patients before they entered the study. The sample consisted of 143 patients (113 female, 30 male) referred from primary care physicians for multiple unexplained somatic complaints.

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TABLE 1. Birth Order Data on 65 Women and 11 Men With Somatization Disorder

Number of Siblings in Family	Ratio of Males to Females in Each Sibship Position												Slater's Index					
													Males		Females		Males and Females	
	1	2	3	4	5	6	7	8	9	10	11	All	Mean	SE	Mean	SE	Mean	SE
1	1:7											1:7	—	—	—	—	—	—
2	1:5	1:3										2:8	0.500	0.500	0.375	0.183	0.4000	0.1633
3	1:3	0:5	0:3									1:11	0.000	—	0.500	0.117	0.4583	0.1145
4	0:3	0:2	1:4	1:0								2:9	0.833	0.167	0.519	0.158	0.5758	0.1355
5	0:2	0:1	0:3	0:3	0:3							0:12	—	—	0.583	0.104	0.5833	0.1036
6			1:1									1:1	0.400	—	0.400	—	0.4000	—
7		0:2	0:1	1:0	0:1	1:1						2:5	0.667	0.117	0.433	0.135	0.5000	0.1091
8		0:2					1:0	0:2				1:4	0.857	—	0.571	0.247	0.6286	0.2000
9				0:1								0:1	—	—	0.375	—	0.3750	—
10				0:1	0:2				0:1			0:4	—	—	0.528	0.123	0.5278	0.1232
11											1:0	1:0	1.000	—	—	—	1.0000	—
12										0:1		0:1	—	—	0.818	—	0.8182	—
13			0:1					0:1				0:2	—	—	0.375	0.208	0.3752	0.2083
Total	3:20	1:15	2:13	2:5	0:6	1:1	1:0	0:3	0:1	0:1	1:0							

As part of this study, the patients underwent a diagnostic interview by a psychiatrist (G.R.S.) to obtain a comprehensive symptom list for each patient. The *DSM-III-R* diagnosis of somatization disorder was based on the symptoms reported during the interview and on an extensive review of the patient's medical records to determine that symptoms were not medically explained. Patients were followed for a period of 2 years. Details have been presented elsewhere (17). In this manner, a group of 76 patients (65 female, 11 male) with somatization disorder was obtained. A second group consisting of 67 patients (48 female, 19 male) who did not fully meet the *DSM-III-R* criteria for somatization disorder (somatizers) was also evaluated for birth order position. To offset the distortion often caused by incomplete sibships in birth order research (10, 11), a sibship was defined as the children born to a mother within 24 years of the birth of her first child. The youngest subject studied was 24 years old, and sibships were presumed complete at the time of sampling. The somatization disorder sample had a mean±SD age of 44.6±9.3 years; the somatizers had a mean age of 45.2±12.9 years.

Birth order may be analyzed using several methods, including the Greenwood-Yule method (18) (which assumes random distribution of numbers in each birth rank within each family size), birth position analysis (19), the Haldane and Smith method (20), and Slater's method (21, 22). For this study, Slater's method was used.

Slater's index is weighed as $(m-1)/(n-1)$, where *m* is the ordinal position and *n* is the number of children born to the same mother. Slater's index values range from 0 to 1, with a mean value in a normally distributed population tending toward 0.5 (21). An observed mean less than 0.5 indicates early birth order position; an observed mean greater than 0.5 indicates late birth order position. The index tends to balance the effect of the overrepresentation of late-born siblings in large families with the overrepresentation of early-born siblings in small families (22). Significant differences are determined by the deviation between the theoretical mean and the observed mean of the weighted frequency distribution of Slater's index divided by the standard error of the mean, where the degrees of freedom equal $n-1$ (Student's t distribution) (6, 19, 21, 23).

Slater's index was determined for the patients with somatization disorder and for the somatizers; analyses were done on each group as a whole and on each group divided into subgroups of men and women. This allowed the study of any possible gender effect on birth order.

RESULTS

Table 1 shows the Slater index values for birth order for the 11 men with somatization disorder, the 65 women with somatization disorder, and the combined group of 76. The Slater index±SE for the somatization disorder group as a whole was 0.5196±0.0466 (t=0.42, df=75, n.s.); for the somatizers it was 0.5602±0.0494 (t=1.2, df=66, n.s.). When the Slater index for the somatizers was compared with the Slater index for the whole somatization disorder group, a nonsignificant difference was obtained (t=0.86, df=142). When the somatization disorder sample was separated into males and females, the Slater index was 0.6257±0.1233 for males (t=0.98, df=10, n.s.) and 0.5013±0.0503 for females (t=0.02, df=64, n.s.). When males and females were considered separately, the Slater index for the somatizers showed nonsignificant differences for males (0.5502±0.0967) (t=0.52, df=18) and for females (0.5636±0.0581 (t=1.10, df=47).

DISCUSSION

Rather than supporting the theory of either an earlier or later birth order position for patients with somatization disorder, this study showed a distribution that would be expected in a random sampling of the general population. Slater's indices for somatization disorder did not show significant deviations from the theoretical mean of 0.5 (table 1). These findings provide no support for the notion that environmental influence on somatization disorder occurs through birth order.

Because of the diagnostic diversity of the subjects in earlier studies, comparisons are difficult to make. However, the study conducted by Morrison (6) provides some of the more reliable data previously published. Morrison showed a significantly earlier birth order position (Slater $\text{index} \pm \text{SE} = 0.3678 \pm 0.0415$, $p < 0.005$) for somatization disorder patients. Over an 8-year period in his clinical practice, he studied 90 women (no men) diagnosed as having somatization disorder by *DSM-III* criteria. The current study also considered the *DSM-III* (in addition to the *DSM-III-R*) criteria for somatization disorder; however, the analyses of the data on women who met the *DSM-III* criteria failed to show that they had an earlier birth order position (Slater $\text{index} = 0.4969 \pm 0.0510$) ($t = 0.06$, $df = 64$, n.s.). One possible source of distortion in Morrison's study is incomplete sibships. Morrison reported that the subjects' mean age was 32.0 years without specifying an age range. Our sample of somatization disorder patients had a mean±SD age of 44.6±9.3 years, with a range of 24–58 years. Morrison's use of a younger age group may have introduced incomplete sibships into his study. By correcting for incomplete sibships, Morrison would likely have found that his somatization disorder patients had an even earlier birth order position. Thus, incomplete sibships cannot account for the difference between Morrison's finding that somatization disorder patients had earlier birth order positions and our finding of random birth order. In addition, potential bias due to reproductive changes in the population (i.e., smaller family sizes over successive generations) can be controlled for by studying a sample of patients within a narrow age range or one generation (11, 12). Our study, with a 34-year age range, met this criterion.

This study supports the earlier findings of Stephens and Kamp (9) and Ziegler et al. (8) that nearly 30% of siblings with hysteria were firstborn or only children. However, our study also indicates that 29% of siblings with somatization disorder are the last born (table 1). This is a statistical trap of birth order analysis that benefits smaller family sizes. According to table 1, when the number of siblings considered is six or more, then none of 23 siblings was the firstborn and 13% ($N=3$) were the last born. However, when the number of siblings considered is five or fewer, 43% ($N=23$) were firstborn and 36% ($N=19$) were last born. Because they are so highly dependent on family size, comparison data on first- and last-born subjects must be carefully interpreted. Slater's index remains a more useful method of comparison, since it tends to balance the effects of overrepresentation in family sizes.

When the Slater indices of the somatizing group were compared with those of the somatization disorder group, no differences existed ($t=0.86$, $df=142$). It has been shown that some somatizing patients will eventually be given a diagnosis of somatization disorder (24). Since both the somatization disorder patients and the somatizing patients had randomly distributed birth orders, even if all of the somatizers develop somatization disorder these data will not be affected.

This study represents the first time that birth order has been investigated using patients who meet the strict diagnostic criteria for *DSM-III-R* somatization disorder and patients diagnosed as somatizers. The study shows that a nonrandom birth order position is not associated with the *DSM-III-R* diagnosis of somatization diagnosis and that sibship positions of somatization disorder patients occur by chance. Thus, although environmental factors may influence the development of somatization disorder, the expression of environmental influence through birth order is unlikely.

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Substituting Nonsomatic for Somatic Symptoms in the Diagnosis of Depression in Elderly Male Medical Patients

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The authors examined the sensitivity and specificity of a modified version of the Research Diagnostic Criteria (RDC) for major, minor, and intermittent depressive disorder in 150 elderly male medical inpatients. Four somatic RDC symptoms were replaced with four nonsomatic symptoms. The sensitivity of the modified criteria was 87%, the specificity was 97%, and 96% of patients were correctly classified. Misclassifications were of mildly depressed patients. These results provide empirical support for the use of alternative, nonsomatic depressive symptoms when somatic symptoms are ambiguous indicators of depression.

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Poor physical health places older adults at greater risk for development of affective disorders. The prevalence of depressive disorders among older adults residing in the community is approximately 2% (1, 2), while studies of elderly medical in- and outpatients (3, 4) have found rates of depression ranging from 15% to 45%.

The diagnosis and treatment of psychiatric comorbidity in this population is made difficult by several factors. First, medical patients prefer to rely on primary care physicians for the detection and treatment of psychological problems (5). Second, detection of such comorbidity by health care givers other than mental health specialists is frequently poor (3, 6–8). For example, in a recent study (3), only 9% of the cases of comorbid depression in elderly inpatients were detected by medical house staff. Third, some somatic signs and symptoms of depression—e.g., appetite or weight change, hypo- or hypersomnia, fatique or loss of energy, and diminished ability to concentrate—also can be symptoms of various medical illnesses and/or drug side effects and are correlates of normal aging. Despite their potential ambiguity, somatic symptoms figure prominently in all current psychiatric diagnostic systems, including *DSM-III-R*, the Research Diagnostic Criteria (RDC) (9), and *ICD-9*.

Nine cardinal signs and symptoms identify major depression: dysphoria, change in appetite or weight, disturbed sleep, fatigue or energy loss, psychomotor agitation or retardation, anhedonia, self-reproach, diminished concentration or ability to make decisions, and suicidal thoughts or behavior. Common associated depressive symptoms are depressed appearance or tearfulness, pessimism, brooding, feelings of inadequacy, self-pity, demandingness or dependency, social withdrawal or decreased talkativeness, nonreactivity to environmental events, resentfulness, complaining, or anger. Endicott (10) suggested that one means for dealing with the nonspecificity of somatic symptoms is the replacement of the four cardinal somatic symptoms with four nonsomatic associated symptoms. Specifically, she suggested replacing change in appetite or weight with tearfulness/depressed appearance, replacing sleep disturbances with social withdrawal/decreased talkativeness, replacing fatigue or loss of energy with brooding/self-pity/pessimism, and replacing diminished ability to think or concentrate or indecisiveness with lack of reactivity to environmental events. We have found no study, however, in which the validity of these alternative criteria has been evaluated.

In the present study we empirically evaluated Endicott's proposal for diagnosing depression in a sample of medically ill older men. The sensitivity and specificity of diagnostic classifications made with the alternative criteria were compared to the sensitivity and specificity based on the standard criteria. We also evaluated the sensitivity and specificity of diagnostic classifications made after eliminating but not replacing the somatic symptoms.

METHOD

The participants in this study were the same as those in a previous study of the prevalence and impact of psychiatric comorbidity in elderly medical patients (3, 11). Briefly, the prospective subjects were 314 randomly selected male patients admitted to general med-

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icine and surgery units of a 499-bed Veterans Administration hospital who were at least 65 years old. After giving informed consent, the subjects were administered the Mini-Mental State examination (12), and 107 (34.1%) patients were eliminated from the study for failing to score above a standard cutoff. An additional 39 (12.4%) refused to participate, and 18 (5.7%) were eliminated because of incomplete protocols. The remaining 150 subjects met all criteria and were included in the study. These 150 subjects had a mean±SD age of 69.3±5.2 years, had 9.9±3.7 years of education, and had an annual income of $9,977±$5,336; 68% were white and 32% were nonwhite.

As reported by Rapp et al. (3, 11), each subject was interviewed with the Schedule for Affective Disorders and Schizophrenia (SADS) (13). The SADS is a semistructured interview involving ratings of numerous psychiatric symptoms, including all of the somatic and nonsomatic cardinal and associated depressive symptoms. For this study, each symptom was scored as either present or absent. In accordance with the methods of the SADS/RDC and *DSM-III-R*, a somatic depressive symptom was rated as absent only if it was judged to be clearly secondary to an organic condition (e.g., loss of appetite after initiation of chemotherapy).

The SADS interview data were then used to assign RDC diagnoses. A diagnosis of major depressive disorder was given if dysphoria plus five of the additional eight cardinal symptoms were present for at least 2 weeks. A diagnosis of probable major depressive disorder required one fewer symptom. A diagnosis of minor or intermittent depressive disorder required dysphoria plus at least two additional symptoms; a probable diagnosis required one fewer symptom.

As reported earlier (3), interrater reliability for RDC diagnoses was evaluated by randomly selecting 10% of the patients to receive concurrent SADS ratings by a second rater, who independently assigned RDC diagnoses. The interviews were conducted by an advanced graduate student in clinical psychology who had extensive training in the use of the SADS/RDC method. The second rater was one of us (S.R.R.), who had considerable experience with the SADS/RDC method. Agreement on the presence or absence of a diagnosis was good for the combined RDC categories (kappa =0.94, p<0.01). The kappa coefficient for depressive diagnoses was 0.89 (p<0.05). Data reported by Rapp et al. (3) also supported the concurrent, convergent, and discriminant validity of the original depressive diagnoses.

For this study, RDC diagnoses of major, minor, and intermittent depressive disorder were reassigned after substituting tearfulness or depressed appearance, social withdrawal or decreased talkativeness, lack of reactivity to environmental events, and brooding, self-pity, or pessimism for appetite or weight change, sleep disturbances, diminished ability to think or concentrate or indecisiveness, and fatigue or loss of energy.

TABLE 1. Correlations Between RDC Somatic Depressive Symptoms and Proposed Alternatives for 150[a] Elderly Male Medical Patients

	Correlation With RDC Somatic Symptom (r)			
Alternative Symptom	Weight/ Appetite Change	Sleep Problems	Loss of Energy or Fatigue	Reduced Concentration
Tearfulness or depressed appearance	0.17[b,c]	0.15	0.35[d]	0.32[d]
Social withdrawal or decreased talkativeness	0.08	0.23[b,e]	0.34[d]	0.33[d]
Pessimism, brooding, or self-pity	0.10	0.41[d]	0.27[b,f]	0.48[d]
Lack of reactivity to environment	0.18[c]	0.07	0.24[e]	0.20[b,e]

[a] Data on one subject missing in a few analyses.

[b] Corresponds to one of the exact item substitutions proposed by Endicott (10).

[c] p<0.05.

[d] p<0.0001

[e] p<0.01.

[f] p<0.001.

RESULTS

Pearson product-moment correlations between the somatic items from the original RDC and the proposed substitutes are presented in table 1. The number of cases used in all correlational analyses was 150 except for a few in which data on one subject were missing. Each correlation between a somatic item and the item Endicott (10) proposed as a substitute for it is identified. These item-to-item correlations are not optimal; indeed, the mean±SD of these four correlations is 0.22±0.04, compared to 0.25±0.12 for the entire table of correlations. By substituting all four of the alternatives for the four somatic items, it was possible to examine the correlation between the total number of positive somatic items and the total number of positive substitute items. This correlation was 0.44 (p<0.0001), indicating that while the new items do not provide redundant information, they are strongly associated with the original items.

While these correlations were low, they compared favorably to the intercorrelations of all RDC symptoms of depression. The mean±SD interitem correlation for all RDC criteria for depression was 0.28±0.10 (range=0.09 to 0.47). In comparison, after substituting the alternative criteria for the somatic criteria, the interitem correlation for all nine criteria was 0.30±0.10 (range=0.10 to 0.53). This suggests that the alternative, nonsomatic symptoms are related to the other criteria for major depressive disorder in the same manner as the somatic symptoms for which they substitute. The low internal consistency of symptoms in

TABLE 2. Diagnoses of Depression in 150 Elderly Male Medical Patients According to RDC and RDC With Alternatives for Somatic Items[a]

	Depressive Diagnoses According to Modified RDC		
RDC Depressive Diagnosis	Major (N=8)	Minor or Intermittent (N=12)	No Depression (N=130)
Major (N=9)	7	2	0
Minor or intermittent (N=14)	1	10	3
No depression (N=127)	0	0	127

[a] Sensitivity=87% (20 of 23); specificity=98% (127 of 130).

this sample of elderly medical patients contrasts with the high intercorrelations among the same symptoms in medically healthy psychiatric patients (13). This is not surprising, however, since many RDC depressive symptoms also represent medical illnesses, drug side effects, and/or normal aging in both depressed and nondepressed patients.

The key question to ask of the proposed substitutes for the somatic criteria is, To what extent does substituting the new criteria result in diagnostic decisions that are comparable to those made with the standard RDC criteria? Table 2 displays the classification of patients into the categories of major depressive disorder, minor or intermittent depressive disorder, or no depression according to the standard RDC criteria and the modified RDC criteria. Of the 150 patients, 144 (96%) were classified in the same way with both sets of criteria. Twenty-three patients received diagnoses of major, minor, or intermittent depressive disorder with the standard criteria, and 20 of them also received depressive diagnoses with the modified criteria (sensitivity=87%). Two of the three patients with false negative diagnoses had received diagnoses of probable minor or probable intermittent depressive disorder with the standard criteria, placing them at the borderline of a diagnosable disorder. Two patients were classified as having major depressive disorder according to the RDC and minor or intermittent depressive disorder according to the alternative criteria. One of these patients had received a diagnosis of probable major depressive disorder when classified with the standard RDC. Thus, of the five subjects given less severe diagnoses with the modified criteria, three had received borderline diagnoses with the standard RDC. One person diagnosed as having intermittent depressive disorder with the RDC was given a diagnosis of major depressive disorder on the basis of the alternative criteria. None of the nondepressed subjects was misidentified with the alternative criteria (specificity=97%, 124 out of 127). Thus, the nonsomatic criteria proposed by Endicott (10) were highly sensitive and specific to depressive disorders.

Another method for dealing with ambiguous somatic symptoms would be to simply eliminate them and use only the five remaining nonsomatic symptoms. To examine this method, we reclassified the patients in the following manner and compared the resulting classifications to those made with the standard criteria. Patients were assigned a diagnosis of depression if 1) dysphoria was present and 2) a set number (one, two, three, or four) of the remaining four cardinal symptoms were present. The sensitivities were 70%, 30%, 17%, and 10%, respectively, and the specificities were 95%, 89%, 87%, and 86%, respectively. Thus, eliminating the somatic symptoms without replacement resulted in poorer classification of patients than when nonsomatic symptoms were substituted.

DISCUSSION

For this sample of elderly male medically ill inpatients, substituting the alternative nonsomatic depressive symptoms suggested by Endicott (10) for the RDC somatic depressive symptoms yielded diagnostic decisions similar to those reached with the standard RDC. The interitem correlations suggested that, rather than substituting these new items on an individual basis, however, all four should be used when a physical cause for the somatic symptoms is suspected.

The availability of a clinical rating instrument that is less reliant on somatic symptoms than current diagnostic systems would be helpful to clinicians and researchers. It may be easier and more accurate to assess brooding, social withdrawal, nonreactivity, etc., than to decide when somatic symptoms are secondary to depression and when they are secondary to the host of other potential causes.

A potential limitation of the present study is the unknown generalizability of these results given the relatively small sample size. Another limitation is the lack of female and younger adult subjects. Differences in the prevalence of somatization between males and females and young adults and old adults, for example, might limit the generalizability of our findings to a female population. It will be important to validate these preliminary findings with different and larger samples.

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Prevalence, Onset, and Clinical Recognition of Panic States in Hospitalized Male Alcoholics

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Alcoholism has been associated with a high prevalence of anxiety and phobic disorders. The authors ascertained the current prevalence of panic disorder and the lifetime prevalence of infrequent panic attacks in 154 male alcoholics in an inpatient alcohol treatment program. Thirteen percent (N=20) gave a lifetime history of panic attacks and 45% (N=9) of these had current panic disorder. Panic attacks preceded or coincided with the onset of problem drinking in 50% (N=9) of the 18 patients with both diagnoses. Only two patients with histories of panic had been previously diagnosed, and none had been treated. Clinical implications of these findings are discussed.

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Panic disorder is a distinct anxiety syndrome characterized by repeated spontaneous attacks of fear accompanied by cardiac, respiratory, gastrointestinal, or neurological symptoms. The lifetime prevalence of panic disorder in the general population is 1%–2%, and women are two to three times more likely than men to be affected (1). Complications of panic disorder include agoraphobia (2) and major depression (3). Patients with infrequent panic attacks resemble those with panic disorder in clinical characteristics and response to sodium lactate infusion (4) and thus form a related, clinically significant group, as recognized in *DSM-III-R*.

Several lines of evidence suggest that panic states and alcoholism are linked. Reich and Chaudry (5) found that 28% of their patients with panic disorder had a history of alcoholism. Others (6, 7) have suggested that alcoholism may represent self-medication of panic disorder and have reported successful use of tricyclic antidepressants to treat symptoms of both panic and alcoholism in patients who have both of these disorders. They found panic states to be infrequently recognized in alcoholics, however.

Other investigators have attempted to define more systematically the relationship between panic states and alcoholism. These studies (8–10) have obtained quite variable results, with the lifetime prevalence of panic disorder ranging between 2% and 21% in hospitalized alcoholics. The inconsistent use of *DSM-III* criteria also makes comparisons and conclusions difficult. The prevalence of agoraphobia has been similarly variable; it has been reported in 12%–41% of inpatient alcoholics (10–12).

Data regarding relative onset of panic and alcoholism are also inconclusive. Panic both predates and follows onset of problem drinking (8–10), and alcohol has been noted to both exacerbate and ameliorate anxiety symptoms (12–16).

It seems clear that there is a relationship between panic states and alcoholism. However, the inconsistent findings to date and the paucity of studies using standard diagnostic criteria make it difficult to be more specific. The present study was undertaken to test the hypotheses 1) that male alcoholic inpatients display a higher than expected prevalence of *DSM-III* panic disorder, agoraphobia with panic attacks, and infrequent panic attacks, 2) that panic symptoms precede alcoholism in the majority of cases, and 3) that panic states in alcoholics are infrequently recognized and treated.

METHOD

The subjects were 154 men admitted consecutively to the Seattle Veterans Administration (VA) Medical Center Addiction Disorders Unit who met the *DSM-III* criteria for alcohol dependence. Their mean±SD age was 42±11 years (range=20–68 years). A detailed drinking history was obtained from all patients by trained staff members and included the patients' retrospective assessments of their ages at the onset of problem drinking (drinking associated with social, work, or marital dysfunction). Hospital charts gave a comprehensive record

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of all diagnoses made and treatments given in the VA system for each subject.

All subjects underwent a screening interview after giving verbal consent. This interview (available from the authors on request) was adapted from the panic and phobia sections of the Diagnostic Interview Schedule (DIS) (17), which uses *DSM-III* criteria, and included questions about history of panic attacks and agoraphobia, frequency and duration of panic symptoms, and situations in which symptoms occurred, including drug and alcohol use or withdrawal. Subjects were not judged to have panic attacks if symptoms occurred exclusively during drug or alcohol intoxication or withdrawal or occurred only in response to specific phobic stimuli.

Eleven subjects with panic and four without panic according to this screening interview gave written informed consent to participate in a still-ongoing second phase of the study consisting of administration of a revised version of the Anxiety Disorders Interview Schedule (18) (ADIS-R) and a lactate infusion at the end of their 4-week hospitalization. The ADIS-R is a standardized instrument for the diagnosis of anxiety disorders, with good interrater reliability for diagnosis of panic disorder; it provided preliminary testing of the reliability of the screening interview for these 15 subjects. Both the ADIS-R and the screening interview were administered by psychiatrists or senior psychiatric residents experienced with *DSM-III* criteria and who were blind to the findings of the other interview. Ten subjects with panic attacks according to the screening interview were excluded from the second phase of the study because they were unwilling to undergo a lactate infusion (N=5), there were medical contraindications for the procedure (N=3), or they were taking psychoactive medications (N=2).

RESULTS

There was good agreement between the screening interview and the ADIS-R on lifetime history of panic attacks (kappa=0.84, $p<0.001$), *DSM-III* panic disorder at the time of the interview (kappa=0.81, $p<0.001$), and lifetime agoraphobia (kappa=1.00, $p<0.0001$). However, the small number of subjects for whom ADIS-R data were obtained may have represented a biased sample. One subject reported panic attacks in the screening interview but was felt to have social phobia according to the ADIS-R and so was not included in the calculation of prevalence rates.

Of the 154 subjects given the screening interview, 20 (13%) reported a lifetime history of panic attacks (including panic disorder and infrequent panic attacks), and nine of these 20 (45% of the 20, or 6% of the total sample screened) had panic disorder at the time of the interview, according to *DSM-III* criteria. Nine (6%) of the subjects had a lifetime history of agoraphobia with panic attacks. Mean±SD ages were 38±3 years (range =30–45 years) for the subjects with histories of panic attacks and 43±12 years (range=20–68 years) for those without panic.

We compared the duration of problem drinking (mean±SD=19±6 years, range=6–25 years) with that of panic symptoms (15±9 years, range=1–34 years) in those for whom data were available (N=18). Nine (50%) of these subjects with histories of panic attacks developed panic after the start of problem drinking, seven (39%) developed panic before the onset of problem drinking, and two (11%) recalled developing both in the same year.

Only two subjects had ever received a diagnosis of panic in the past. Both were currently having panic attacks, but neither had ever been treated for panic. Twelve of the 20 subjects with histories of panic attacks reported a family history of alcoholism. One of the 12 also had a family history of depression. No subject gave a family history of panic attacks.

The 10 subjects with histories of panic confirmed by the ADIS-R reported high lifetime rates of affective and substance use disorders. Seven (70%) gave histories of major depression, although only one was currently depressed. Of these seven, anxiety predated depression in six and was considered the primary problem in five. Seven subjects (70%) had histories of multiple drug abuse. All had histories of panic independent of drug intoxication or withdrawal. However, onset of panic attacks occurred with amphetamine withdrawal in one subject and with alcohol and marijuana use in another.

DISCUSSION

Our data demonstrate that panic states are fairly common in male alcoholic inpatients, that they may, in some cases, precede the onset of problem drinking, and that they are usually unrecognized and untreated in this population. The prevalence rate of 6% for current panic disorder that we found is considerably higher than the 0.3%–0.8% 6-month prevalence reported for males in the general population (19), which is consistent with Quitkin et al.'s assertion (6) that the two disorders commonly coexist. This comparison must be interpreted cautiously, however, since the two groups are not strictly comparable. Studies using control groups of male nonalcoholic inpatients or male alcoholic outpatients are necessary to investigate whether inpatient status, rather than alcoholism, influences the rate of panic states.

The rate of current panic disorder in this study was very similar to the 5% rate found by Hesselbrock et al. (8). Twenty-one percent of 48 patients interviewed by Bowen et al. (10) had panic disorder. This high rate may be due to these authors' more heterogeneous sample, which included women. The 45.8% prevalence of current major depression that they found suggests that their sample may have been weighted toward alcoholics with coexisting psychopathology. It is also unclear whether subjects with panic attacks during withdrawal only were excluded. Weiss and Rosenberg (9) reported a prevalence rate of only 2% for panic disorder, perhaps because subjects with major affective disorders were excluded.

The 6% lifetime prevalence of agoraphobia with panic attacks in our sample is lower than previously reported rates of agoraphobia in alcoholics (10–12), probably because all our subjects were male and we did not include agoraphobia without panic attacks. Two studies that assessed agoraphobia with panic attack (9, 10) reported rates of 1% and 12%.

In the present study, drinking histories and interviews regarding panic symptoms were conducted at different times by different personnel to avoid possible bias in patient reporting of order of onset and possible causal relationships. As a result, we can only comment on order of onset rather than causality. Thirty-nine percent of our patients recalled onset of problem drinking subsequent to development of panic attacks, while 11% developed the two conditions in the same year. This is not appreciably different from the mixed results of prior studies (8–10). Clearly, alcoholism does not always develop as a complication of panic states when both conditions coexist. The hypothesis that alcoholism develops as self-medication for panic in these patients must therefore be questioned.

Any attempts to determine whether underlying vulnerability to panic leads to alcoholism is limited by the fact that retrospective recall of onset of an illness like alcoholism is influenced by many factors. The present study used independent assessments of onset of problem drinking and of panic symptoms to reduce bias in subject reporting but was limited by the lack of third-party confirmation of drinking histories. In the future, use of information from a variety of sources to construct a longitudinal, preferably prospective, picture of the development of alcoholism over time (20) could elucidate the relative contributions of different possibly predisposing influences, and individuals with alcoholism secondary to panic attacks could be more readily distinguished.

A major confounding factor in the study of panic attacks in alcoholics that we identified in the present study was the high rate of multiple drug abuse. Since use of stimulant drugs in particular has been associated with the onset of panic attacks (21), future studies should take this factor into account.

The other significant finding of this study was that only two of 20 subjects with clear-cut spontaneous panic attacks had ever received a diagnosis of panic disorder, panic attacks, or agoraphobia. Neither of these two had ever been treated for panic. It seems that in spite of the fairly high prevalence of panic states among inpatient alcoholics, these conditions are still not recognized by those treating alcohol dependence. This is unfortunate, since panic attacks are treatable with medication that has low potential for abuse (22).

We recommend taking a careful history regarding panic states in all alcoholics, especially drug alcohol- and drug-free periods, to facilitate appropriate recognition and management of these treatable disorders.

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Sleep Panic Attacks: New Clinical Findings and Theoretical Implications

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Forty-five panic disorder patients and 26 normal control subjects were surveyed regarding their histories of sleep panic attacks, insomnia, and vulnerability to exogenous panic stimuli. Sixty-nine percent (N=31) of the patients reported having experienced sleep panic at some time in their lives, and 33% (N=15) of the patients experienced recurrent sleep panic. The implications of these findings for the management of panic disorder are discussed.

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Considerable progress has been made in recent years in elucidating the psychobiology and treatment of panic disorder. Nevertheless, much debate remains regarding the fundamental nature of the condition. One problem inherent in studying panic disorder is that panic attacks, thought by many investigators to be its core symptom, occur episodically and, by definition, at times unpredictably. Because of this situation, it has been convenient for researchers to exploit the greater sensitivity of panic patients to some anxiogenic or activating stimuli. Various biological theories of panic disorder have been derived from studies involving the induction of panic attacks with pharmacological and physiological agents, including sodium lactate (1, 2), caffeine (3, 4), yohimbine (5, 6), isoproterenol (7), and carbon dioxide (8, 9). A criticism of the specificity of these models for panic has been the observation that greater basal physiological and possibly psychological arousal can be predictive of subsequent panic (2, 10). A relationship of panic to preexisting heightened arousal is also suggested by the frequent occurrence of panic attacks, preceded by anticipatory anxiety, in phobic situations. These observations lend support to a continuum theory of anxiety, advocated by some investigators, with panic at the most severe end of the anxiety spectrum (11).

A lesser known but equally important phenomenon is panic attacks preceded by states of diminished arousal. Adler et al. (12) have characterized relaxation-induced panic and have suggested, as we have (13, 14), a relationship between this phenomenon and sleep-related panic. Accumulating evidence from our laboratory also suggests that sleep panic attacks emerge from non-REM sleep, an observation that supports the spontaneous nature of some panic attacks (13–16). An interesting observation from our investigations is that sleep panic attacks typically arise during the transition toward early delta sleep, i.e., during a state of diminishing arousal (16).

Thus, theories regarding the evolution of panic anxiety need to account for panic emerging from settings of both elevated *and* diminished levels of arousal. Consideration of the aforementioned observations raises the possibility that an impairment in the regulation of change in psychophysiological states of arousal is an underlying pathological mechanism in panic disorder.

The purpose of this report is to elucidate the relationship of different states of arousal to the onset of panic attacks in panic disorder patients. Sleep represents an unequivocal state of diminished arousal relative to waking states. Therefore, we examined the prevalence of sleep panic and the relationship of sleep panic to several subjective sleep variables and putative exogenous triggers of panic attacks (17).

METHOD

A survey assessing sleep panic attacks, insomnia, and vulnerability to exogenous panic stimuli was administered to 45 patients (32 female and 13 male) meeting the *DSM-III-R* criteria for panic disorder. To ensure that our data were representative of a general clinical population of panic patients, patients were recruited from three private practices in the greater Washington, D.C., metropolitan area that specialize in the treatment of anxiety disorders. The survey was administered to each consecutive patient seen in these settings by the treating physicians during the time of the study. This method facilitated a random sampling of patients within these treatment settings and a 100% rate of response. Symptoms meeting the diagnostic criteria were elicited by the survey and confirmed by the treating physician. A number of these patients were

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TABLE 1. Nature and Prevalence of Sleep Disturbances in Panic Patients and in Normal Control Subjects

	Control Subjects (N=26)				Panic Patients (N=45)				Analysis			
	Had Recurrent Disturbance		Ever Had Disturbance		Had Recurrent Disturbance		Ever Had Disturbance		Recurrent		Ever	
Disturbance	N	%	N	%	N	%	N	%	χ^2 (df=1)	p	χ^2 (df=1)	p
Panic												
Wake	0	0	2	8	40	89	45	100	52.87	<0.001	62.64	<0.001
Sleep	0	0	2	8	15	33	31	69	11.01	<0.001	24.88	<0.001
Insomnia												
General	9	35	25	96	30	67	44	98	6.83	<0.009	0.17	n.s.
Initial	11	42	24	92	24	53	43	96	0.79	n.s.	0.28	n.s.
Middle	6	23	22	85	30	67	42	93	12.59	<0.001	1.33	n.s.
Late	8	31	18	69	34	76	41	91	13.76	<0.001	5.60	<0.02

treated by us, which enabled further verification of the clinical phenomenology.

The panic disorder patients had a mean±SD age of 37.6±11.0 years (range=22–55). Eighty percent (N=36) of these patients also met the *DSM-III-R* criteria for moderate to severe agoraphobia, and 58% (N=26) reported past episodes of major depression, although none of the patients had major melancholic depression at the time of the study. Participating patients were in various stages of treatment and were asked to respond to questions in terms of their typical experience. For the purpose of comparison and to provide normative data, we also administered the survey to 26 normal subjects (18 female and eight male) with a mean±SD age of 34.1±7.7 years (range=20–51). The normal subjects were recruited primarily from the clinical staff of the National Institute of Mental Health and were free of psychiatric illness. Patients and control subjects did not differ significantly with regard to age or gender distribution.

The survey contained four items related to subjective assessment of the quality of sleep (e.g., insomnia) and five items related to factors associated with the triggering of panic attacks (e.g., caffeine, exercise). These items were presented in a statement format (e.g., "I have difficulty falling asleep"; "I experience panic from caffeine"). Subjects were given five options from which to choose in responding to each statement: never, rarely, occasionally, frequently, or almost always. The statement "I experience panic from drinking a lot of water" was included to assess for nonspecific endorsement of items. On the basis of these nine items, the lifetime prevalence of each symptom (e.g., sleep panic) or condition (e.g., caffeine-induced panic) was considered positive if the subject responded with any of the options except "never."

Since almost everyone has experienced at least one episode of disturbed sleep, we hypothesized a priori that determining the lifetime prevalence of sleep-related events alone might provide low specificity in discriminating between the panic disorder patients and the normal control subjects. Therefore, in addition to investigating the lifetime prevalence of various sleep-related events, we also investigated the predominance of these symptoms and conditions in terms of their regular and pervasive impact upon the individual. Thus, responses were categorized as being infrequent (never or rarely experienced) or recurrent (occasionally, frequently, or almost always experienced).

Using chi-square analysis, we made categorical comparisons between the patients and the control subjects of the various sleep disturbances. These comparisons were made both in terms of positive or negative lifetime history (i.e., whether the symptom had ever occurred at any point during the subject's life) and in terms of whether the symptom was an infrequent or recurrent event. In addition to the comparison of the prevalence of sleep panic in patients and control subjects, we used chi-square analysis to make categorical comparisons between the patients with and the patients without histories of sleep panic on the remaining variables.

RESULTS

Eighty-nine percent of the patients, but none of the control subjects, reported having recurrent panic attacks when awake (see table 1). Thirty-three percent of the patients, but no control subjects, reported recurrent sleep panic attacks. Sixty-nine percent of the patients reported ever having had a sleep panic attack. This compares to 8% (N=2) of the normal control group; both of these subjects reported sleep panic as rare occurrences. Two control subjects also reported the rare occurrence of wake panic attacks.

As expected, lifetime occurrences of the various insomnia patterns were common in both groups (see table 1). Recurrent middle and late insomnia were more common in the patients than in the normal control subjects. The prevalence of recurrent initial insomnia, however, was not significantly different between the patients and the control subjects.

Caffeine was most frequently noted as a recurrent trigger of panic attacks (62%, N=28), followed by "not getting enough sleep" (sleep deprivation) (56%,

TABLE 2. Characteristics of 45 Panic Disorder Patients With or Without Lifetime Histories of Sleep Panic

Recurrent Symptoms and Triggers of Panic Attacks	Patients Without Sleep Panic (N=14)		Patients With Sleep Panic (N=31)		Analysis	
	N	%	N	%	χ^2 (df=1)	p
Symptom						
General insomnia	5	36	24	77	7.32	<0.007
Initial insomnia	4	29	20	65	5.01	<0.03
Middle insomnia	7	50	24	77	3.38	<0.09
Late insomnia	7	50	26	84	5.66	<0.03
Wake panic	13	93	27	87	0.32	n.s.
Depression	4	29	22	71	7.15	<0.008
Agoraphobia	10	71	25	81	0.49	n.s.
Trigger of panic attacks						
Relaxation	3	21	19	61	5.99	<0.01
Sleep deprivation	3	21	22	71	9.59	<0.002
Caffeine	8	57	20	65	0.22	n.s.
Exercise	4	29	15	48	1.53	n.s.
Water	1	7	2	6	0.07	n.s.

N=25), relaxation states (49%, N=22), and exercise (42%, N=19). Only 7% (N=3) of the patients endorsed the statement that drinking a lot of water was associated with triggering panic. The low level of nonspecific endorsement for this item adds internal validity to the findings that caffeine, sleep deprivation, relaxation, and exercise could induce panic in a substantial proportion of our patient sample.

All types of insomnia were more prevalent in the patients with histories of sleep panic than in the patients who had never had sleep panic (see table 2). Although we found no differences between these groups with respect to recurrent wake panic and agoraphobia, a lifetime history of depression was more frequently noted by the patients with sleep panic. Relaxation states and sleep deprivation were significantly more frequently reported as panic precipitants by the patients with sleep panic. There was no difference between the two groups of patients with respect to caffeine, exercise, and excessive water drinking.

DISCUSSION

Although previous studies have reported that insomnia or sleep disturbance is common in panic disorder patients (13, 16, 18–20), this study was the first, to our knowledge, to examine the prevalence of sleep panic attacks. It appears that the majority of panic disorder patients in clinical treatment have experienced sleep panic. A subgroup of patients appear to have sleep panic as a recurrent and, in some cases, predominant symptom.

As in previous studies, we found a relatively high prevalence of insomnia in panic disorder patients. What was not expected, however, was the greater prevalence of awakening from sleep (middle insomnia) and early morning awakening in the panic disorder patients, whereas difficulty falling asleep did not distinguish the patients from the control subjects. These findings support the distinctiveness of the clinical features of panic disorder from a "normal" spectrum of transient anxiety experiences that often include difficulty falling asleep. The finding also supports the notion of a phenomenological overlap of panic disorder with depression. Interestingly, however, most studies have not found that REM latency is reduced in either patients with panic disorder or patients with nonspecific or "mixed" anxiety syndromes as has been demonstrated in depression (16, 20–22).

It is of further interest that the patients who reported sleep panic tended also to report panic induced by relaxation and sleep deprivation. In contrast, we did not find an association between sleep panic and the other exogenous panic triggers we surveyed. The association of sleep, relaxation, and sleep deprivation (i.e., drowsiness) with eliciting panic is intriguing because it suggests that a subgroup of panic disorder patients may be specifically vulnerable to diminished arousal as a trigger of panic attacks.

The study had several limitations. The frequencies reported are subjective estimates rather than specific or objective numerical frequencies. The inclusion of data on patients' wake panic attacks, however, provides a point of reference regarding the relative frequency of sleep panic. Although these data came from retrospective reports, we have found that patients' estimates of the frequency of their panic attacks are relatively reliable. The information obtained by the survey also did not allow for systematic assessment of the phenomenology of sleep panic attacks. The survey did elicit open-ended descriptions of the episodes, which were consistent with the *DSM-III-R* criteria for panic attacks in panic disorder. Moreover, we have recently assessed the clinical features of sleep panic in a group of patients participating in a prospective sleep study, and results from that investigation (13, 16) corroborate the self-report findings of the present study. In both studies, sleep panic attacks featured apprehension or fear upon awakening and were often characterized as "jolting" or "shocking" the patient from sleep. These episodes were not associated with dream recall. The specific symptoms of these sleep panic attacks overlapped considerably with those of the same patients' wake panic attacks. The most frequent symptoms of sleep panic were palpitations, followed by dyspnea and flushing. The sleep panic attacks were somewhat less likely than wake panic to feature extreme fears such as fear of dying or going crazy, although fear of falling asleep was not an infrequent complaint of some patients with recurrent sleep panic attacks. In fact, the patients with initial insomnia appeared to develop a fear of falling asleep as a secondary consequence of sleep panic attacks—a process analogous to the development of agoraphobia following wake panic attacks.

The aforementioned features of sleep panic attacks tend to distinguish these events from classic descriptions of night terrors in children, which feature confusion during, and amnesia for, the episode (23). However, since descriptions of adults experiencing night terrors do suggest some areas of overlap with panic disorder (24), the relationship of night terrors and sleep panic attacks is worthy of further investigation.

The findings of the present study add to an evolving picture of sleep panic in panic disorder. In addition to the phenomena of sleep panic that we have noted, we have also examined the sleep EEG correlates of sleep panic attacks. Such attacks are typically preceded by non-REM sleep, a finding consistent with the statements by the patients that their sleep panic attacks were not related to dreaming. Moreover, patients with sleep panic attacks report that they can easily distinguish between these attacks and episodes of dreaming or nightmares.

In a separate study we also documented several case reports of patients whose sleep panic attacks, not wake panic attacks, heralded the onset of their illness. Moreover, as our interest in sleep panic has become increasingly recognized within the local medical community, we have been referred an increasing number of patients whose predominant complaint is sleep panic attacks.

Thus, both our clinical experience and the findings of the current study suggest that sleep panic attacks may be a common problem in patients with panic disorder. In addition, patients with sleep panic appear to have a greater rate of insomnia and depression than do panic disorder patients without sleep panic. The data also suggest that sleep deprivation and its attendant drowsiness may play a role in exacerbating symptoms in some panic disorder patients with sleep panic attacks. In fact, in a previous investigation from our section (25), we found that intentional sleep deprivation exacerbates anxiety symptoms, including the triggering of panic attacks, in panic disorder patients. Considered together, these converging lines of evidence indicate that many patients' sleep panic attacks, insomnia, sleep deprivation, and wake panic attacks may be intimately related to one another in a positive feedback loop. As a result, the careful assessment and treatment of these interrelated phenomena may be important in the overall management of panic disorder patients.

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Comparison of Adolescent- and Adult-Onset Unipolar Depression

Thomas H. McGlashan, M.D.

The author compared the longitudinal clinical profiles of patients with adolescent-onset (N=20) and adult-onset (N=38) unipolar depression. The findings support the validity of subtyping depression by age at onset and comorbid substance abuse.

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Age at onset may define homogeneous subgroups of unipolar depressed patients. Weissman et al. (1) found three factors among depressed patients that were associated independently with greater risk of major depression in first-degree relatives: early age at onset, comorbid anxiety disorder, and secondary alcoholism. Weissman et al. (2) also found that patients with onset of depression at 20 years of age or younger had the highest familial loading, whereas patients with an onset at 40 years or older had familial aggregation rates similar to those of normal control subjects. Noting that most studies have used age 40 as the cutoff between early and late onset, Weissman et al. suggested revising the cutoff age to 20. Recent studies have replicated the relationship between age at onset and familial prevalence of depression (3) and bipolar disorder (4).

In addition to family pedigree studies, long-term outcome can provide independent validation of putative etiologically homogeneous subgroups. If early age at onset identifies a homogeneous subgroup that "breeds true" in families, might it also identify a cohort with a distinctive clinical profile and long-term outcome? We tested this question using long-term follow-up data collected on unipolar depressed patients from the Chestnut Lodge follow-up study (5).

METHOD

The study subjects consisted of psychiatric inpatients at a long-term residential treatment facility who were discharged between 1950 and 1975 and who underwent follow-up examination an average of 15 years later (range=2–32 years). Two sets of data—baseline diagnostic/demographic and outcome—were collected independently by different research teams (5). After informed consent was obtained, outcome data were collected from interviews (mostly by telephone) with the subjects and/or significant others. The information gathered was sufficient to provide reliable assessment of multiple outcome dimensions over the entire period of time since discharge (5). Baseline clinical dimensions, such as demography, family history, premorbid functioning, manifest illness, and illness course up to and including index admission, were rated retrospectively from medical record abstracts. On the basis of these data, all study patients were rediagnosed according to current operational diagnostic systems.

Fifty-eight patients who satisfied the *DSM-III* criteria for unipolar depression were studied. Of these, 20 had had an adolescent onset (at or before 19 years of age) and 38 had had an adult onset (at or after 20 years of age). We located and obtained follow-up data on 16 and 28 of them, respectively. The groups were tested across three categories of variables: demographic/predictor, diagnostic, and outcome. Statistical analyses used chi-square tests for categorical variables and t tests (two-tailed) for continuous variables. Sample sizes fluctuated depending on the variable tested. Significance was set at $p<0.05$.

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TABLE 1. Baseline and Outcome Dimensions of Patients With Adolescent-Onset or Adult-Onset Unipolar Depression

	Adolescent Onset		Adult Onset				
Variable	Mean	SD	Mean	SD	t	df	p
Baseline[a]							
Psychopathology of father (0=worst; 4=best)	1.2	0.8	2.1	0.7	−3.7	48	<0.0001
Prior hospitalizations	1.4	1.1	2.2	1.8	−2.1	54	<0.04
Premorbid functioning							
Sexual adjustment (Phillips scale: 6=worst; 0=best)	2.9	1.2	1.7	1.5	3.2	55	<0.002
Educational level (7=lowest; 1=highest)	3.5	1.0	2.2	1.0	4.8	54	<0.0001
Acquisition of skills (0=worst; 4=best)	2.6	0.8	3.3	0.8	−3.3	55	<0.002
Work competence (0=worst; 4=best)	2.4	1.1	3.1	0.8	−2.5	44	<0.02
Outcome[b]							
Work time during follow-up (0=worst; 4=best)	3.1	1.2	2.1	1.5	2.1	42	<0.04
Alcohol problems during follow-up (0=worst; 4=best)	3.1	1.0	2.0	1.6	2.6	41	<0.01
Sum global outcome (0=worst; 16=best)	12.3	3.6	9.8	4.1	2.0	41	<0.05

[a] Adolescent onset, N=20; adult onset, N=38.

[b] Adolescent onset, N=16; adult onset, N=28.

RESULTS

Baseline Comparisons

The average age at onset was 16 years for the 20 adolescent-onset unipolar patients and 30 years for the 38 adult-onset unipolar patients. These differences, as well as those for age at first hospitalization (21 and 34 years, respectively) and for age at index hospitalization (23 and 37 years), were highly significant ($p<0.0001$) by definition.

Females predominated in both cohorts (60%, or N=12, in the adolescent-onset group and 74%, or N=28, in the adult-onset group), but the gender differences were not significant ($\chi^2=0.6$, df=1). As expected, a significantly higher percentage of the adult-onset cohort (68%, or N=26) than of the adolescent-onset cohort (10%, or N=2) were married or had been married ($\chi^2=15.6$, df=1, $p<0.0001$).

The fathers of the adolescent-onset group were more disabled psychologically (see table 1). Our medical records, however, were not sufficiently detailed to determine the diagnostic nature of these disabilities. We found no differences between cohorts in the rates of familial schizophrenia, mania, depression, and psychiatric hospitalization.

Differences in premorbid functioning were frequent. The adult-onset group scored consistently better than the adolescent-onset group on measures of sexual adjustment, academic achievement, acquisition of instrumental skills, and work competence (table 1).

Despite the gap in ages at onset, the two cohorts differed strikingly little on morbid dimensions of psychopathology. The adult-onset group had been hospitalized more frequently before index admission, but both groups had previously spent comparable amounts of time in outpatient and inpatient treatment settings. Adolescent- and adult-onset unipolar patients were not different with respect to signs or symptoms of mania, depression, delusions, hallucinations, and suicidal ideation or activity. They were different, however, with respect to substance abuse; 50% (18 of 36) of the adult-onset cohort and only 11% (two of 19) of the adolescent-onset cohort were rated as having substantial substance abuse problems, mostly with alcohol, in the year before index admission ($\chi^2=6.8$, df=1, $p<0.01$).

Outcome Comparisons

At follow-up, a significantly higher percentage of the 28 adult-onset unipolar patients than of the 16 adolescent-onset patients had been or were married (86%, or N=24, and 40% (six of 15), respectively; $\chi^2=7.6$, df=1, $p<0.006$) and were parents (68%, or N=19, and 19%, or N=3, respectively; $\chi^2=8.0$, df=1, $p<0.005$). The adult-onset patients also had significantly more alcohol-related problems and worked less steadily than the adolescent-onset patients (table 1). The adolescent-onset cohort, however, had better global functioning (the sum of the individual outcome dimensions of symptoms, hospitalization, and work and social functioning) over the entire follow-up period than the adult cohort.

The degree to which these outcome differences could be accounted for by alcohol abuse was tested by dividing the adult-onset cohort into those with (N=13) and those without (N=15) alcohol abuse in the year before index admission and comparing their outcomes to that of the adolescent-onset cohort (N=16) with a one-way analysis of variance (ANOVA) and Scheffé's post hoc pairwise comparisons. The results for marital and parental status were virtually unchanged. The adolescent-onset group still had the highest scores on the measures of work time (adolescent onset, mean±SD=3.1±1.2; adult onset with alcohol abuse, 1.8±1.5; adult onset without alcohol abuse, 2.5±1.6; F=3.20, df=2, 41, $p<0.06$; all post hoc comparisons nonsignificant by Scheffé test) and sum global outcome (adolescent onset, 12.3±3.6; adult onset with alcohol abuse, 8.8±3.8; adult onset without alcohol abuse, 10.7±4.3; F=2.90, df=2, 40, p<0.07; all post hoc comparisons nonsignificant by Scheffé test). The overall significances were reduced to trend levels, and all pairwise comparisons were nonsignificant, in part because of loss of cell sample size and degrees of freedom. Clearly, however, the data suggest that adult-onset depressed patients with alcohol problems had the poorest outcomes and contributed substantially to the overall differences in outcome between the adult-onset and adolescent-onset cohorts noted in table 1.

DISCUSSION

The mean age of 30 years for our adult-onset patients would have been regarded as an early age at onset in most previous studies. The relative youth of both of our cohorts, therefore, could have minimized differences and raised the likelihood of type II error (false negative results).

Another shortcoming of our study derives from our database for family ratings. Much of our medical record information regarding families was incomplete, anecdotal, and not rigorous in its nosologic orientation. Our finding of no difference in family history of affective disorders between the early- and late-onset cohorts, therefore, cannot be considered a robust test of Weissman et al.'s (1, 2) hypothesis. We found some supporting evidence in the form of more severe levels of psychopathology among the fathers of our adolescent-onset cohort, but the records were not sufficiently detailed for us to assign diagnoses reliably.

The two groups were quite different before the onset of illness. The adult-onset group was consistently superior in social, sexual, and academic/occupational functioning, probably because illness disrupted normal midadolescent growth and development in the adolescent-onset cohort. Psychopathology derails adolescents' pursuit of relationships and development of instrumental capacities and does so with sufficient invasiveness to require long-term hospitalization. Therefore, the poor premorbid functioning of the adolescent-onset group probably reflects morbidity rather than premorbidity.

With respect to psychopathology, the clinical phenomena in the adolescent-onset and the adult-onset unipolar syndromes were similar except for greater alcohol abuse in the adult-onset cohort. Alcohol abuse was so prevalent, in fact, that our adult-onset group may have had approximately the same characteristics as the subgroup diagnosed by Weissman et al. (1) as having major depression with secondary alcoholism.

Our adolescent-onset unipolar patients were quite different from adolescent-onset *bipolar* patients, who are frequently noted to exhibit psychotic symptoms, including first-rank symptoms, delusions, ideas of reference, hallucinations, and signs of behavioral dyscontrol such as assaultiveness and trouble with the law (6). Adolescent-onset bipolar patients are also more likely to be diagnosed as having schizophrenia or schizoaffective disorder (6), unlike our unipolar adolescent-onset group, which was quite homogeneous in its diagnoses of affective disorders.

Some differences in outcome (e.g., marital status, parental status, and alcohol abuse) probably reflected baseline inequities carried forward. The other outcome differences (work time and overall global functioning) were less expected, given the distinctly inferior baseline functioning of the adolescent-onset unipolar patients. Roughly the same reversal from baseline to follow-up occurred for our adolescent-onset bipolar cohort (6). Such equalization of baseline differences by the time of follow-up also has been reported elsewhere for early- and late-onset bipolar patients (7, 8). To our knowledge, this constitutes the first such report for unipolar patients.

As our second ANOVA suggested, the work and global outcome differences may have been accounted for largely by the differences between the adolescent-onset patients and the adult-onset patients with substance abuse. These differences, however, only reached trend levels of significance. Thus, this study may be viewed as a preliminary comparison of two of the affective disorder subtypes identified by Weissman et al. (1): early (adolescent)-onset major depression and adult-onset major depression with secondary alcoholism. Our analysis of the long-term clinical profiles suggests that this distinction deserves further study. Amalgamation of our results with those of Weissman et al. (1) suggests that adult-onset major depression with secondary alcoholism may be characterized by a low familial loading of affective disorder and a good premorbid profile but a poor or chronic long-term course and outcome, perhaps because of the comorbidity. Adolescent-onset major depression, on the other hand, may be characterized by a high familial loading of affective disorder and severe disruption of adolescent growth and development but low comorbidity and relatively good long-term course and outcome.

Although this largely retrospective investigation should be interpreted with caution, it suggests that age at onset and comorbid substance abuse may define unipolar subtypes with distinctive longitudinal clinical profiles. An optimal test of these findings, however, would use repeated prospective longitudinal assessments.

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Psychiatric Syndromes in Adolescent Substance Abusers

Lawrence DeMilio, M.D.

Conduct disorder, major depressive episode, and the combination of attention deficit, hyperactivity, and impulse disorder were the most prevalent diagnoses after detoxification among 57 adolescents consecutively referred to an inpatient facility for treatment of substance abuse and other concurrent psychiatric disorders.

(Am J Psychiatry 1989; 146:1212–1214)

Although there are clinical reports describing the rates of various psychiatric syndromes among groups of adult patients who acknowledge out-of-control substance abuse patterns (1–3), there is less information on adolescent patients who are labeled chemically dependent. Several authors (4, 5) have described disruptions in the adolescent developmental tasks of identity and independence definition, in the attainment of educational skills, and in the cohesion and roles of family systems that substance abuse patterns often produce. However, there are few data on specific correlations or temporal relationships between substance abuse patterns and specific adolescent psychiatric syndromes.

Kashani et al. (6) reported significantly higher rates of alcohol dependence and amphetamine abuse in adolescent outpatients who abused substances and who had double depression, a severe and chronic form of adolescent depression. Famularo et al. (7) reported a high rate of affective disorders among 10 preadolescents who were alcohol abusers.

Gittelman et al. (8) reported that the diagnoses of conduct disorder, substance abuse, and attention deficit disorder with hyperactivity aggregated significantly in adolescents who had continued attention deficit disorder with hyperactivity, suggesting that children with attention deficit disorder with hyperactivity are at high risk for the development of substance abuse.

In this report I will summarize findings on the coincidence of specific *DSM-III* diagnoses among a group of adolescents referred for inpatient treatment for substance abuse and other concurrent psychiatric disorders.

METHOD

Using strict *DSM-III* criteria, I systematically evaluated and diagnosed 57 adolescents consecutively admitted to two facilities for treatment of substance abuse and other concurrent psychiatric disorders. The mean age of the patients was 16.2 years (range=14–18); two of the patients were 14 years old, 18 were 15, 16 were 16, nine were 17, and 12 were 18. Forty of the patients were boys and 17 were girls. During the evaluation phase of admission, I administered both open and semistructured interviews of patients and their families as well as the Structured Clinical Interview for *DSM-III* (SCID) (9). In addition, the first 44 patients completed an educational test battery consisting of the WISC-R, the Wide-Range Achievement Test, and a paragraph writing sample.

To avoid drug washout phenomena, I finalized the diagnoses at the beginning of the third week of inpatient stay. Elevated hyperactivity scores on Conners' parental questionnaires (10) were required in addition to *DSM-III* criteria to finalize the diagnosis of attention deficit disorder with hyperactivity.

Adolescents were asked to identify their drug of choice—the one substance they sought, obtained, and used in preference to others.

RESULTS

Twenty-four (42%) of the 57 patients met diagnostic criteria for conduct disorder. The next most frequent axis I diagnosis was major depressive episode, diagnosed in 20 (35%) of the patients at the start of the third inpatient week; 10 (18%) additional patients were given a diagnosis of major depressive episode on admission, but this disorder had cleared after 2 weeks of abstinence. I felt that this transient depressive episode could best be considered a psychoactive-substance-induced affective disorder. The next most frequent diagnoses were attention deficit disorder, residual type, and attention deficit disorder with hyperactivity, present in eight (14%) of the patients, and intermittent explosive disorder, present in four (7%) patients, yielding a 21% overall rate of attention deficit, hyper-

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TABLE 1. *DSM-III* Diagnoses[a] and Drugs of Choice of 56 Adolescents Hospitalized for Substance Abuse and Other Concurrent Psychiatric Disorders

	Alcohol or THC, Then Cocaine (N=25)		THC Only (N=5)		Alcohol Only (N=15)		Cocaine Only (N=11)	
Diagnosis	N	%	N	%	N	%	N	%
Major depressive episode (N=20)	10	40	1	20	5	33	4	36
Transient depression (N=10)[b]	4	16	1	20	4	27	1	9
Attention deficit, hyperactivity, or impulse disorder (N=12)	6	24	2	40	2	13	2	18
Social phobia or avoidant personality disorder (N=4)	2	8	0	0	0	0	2	18
Schizophreniform disorder (N=4)	2	8	0	0	1	7	1	9
Dysthymic disorder (N=6)	1	4	1	20	3	20	1	9

[a] Not all diagnoses are listed.

[b] Patients diagnosed as having major depressive episode at admission but not at the beginning of the third week of hospitalization.

activity, or impulse disorder. Schizophreniform disorder was diagnosed in four (7%) of the patients, six (11%) met criteria for dysthymic disorder, and four (7%) met criteria for social phobia or avoidant personality disorder. Although it is not technically correct to assign personality disorder diagnoses in this age group, nine (16%) of the 57 patients demonstrated very prominent features of personality disorders. Two of these patients had schizoid, two borderline, two paranoid, two narcissistic, and one schizotypal personality disorders. One of the patients was not given a diagnosis. Each patient could be given more than one diagnosis.

Educational lags of two grade levels or more in at least one academic subject were found in 27 (61%) of the 44 patients who completed the educational test battery.

The most common pattern of drug preference, cited by 25 (44%) of the patients, was that they originally preferred alcohol and/or tetrahydrocannabinol (THC) but then preferred cocaine. Five (9%) of the patients preferred only THC, 15 (26%) preferred only alcohol, and 11 (19%) preferred only cocaine; one patient did not indictate a preference.

To see if the identified drug of choice correlated with any psychiatric disorder, I compared the rate of the major diagnoses in the adolescents grouped by their drug of choice (table 1). There was a much higher ratio of major depressive episode (lasting depression) to transient depression among adolescents who preferred only cocaine or initially preferred alcohol and/or THC and then preferred cocaine. The rates of lasting depression and transient depression were more evenly divided among adolescents who preferred only alcohol or only marijuana.

DISCUSSION

It was my intention in this study to report on possible relationships between adolescent substance abuse and certain specific psychiatric disorders in adolescents. Fully half of this consecutive admission sample initially met criteria for serious depressive disorder. About a third of these patients demonstrated a transient depression that cleared spontaneously after a 2-week period of abstinence. However, 20 (35%) of the 57 patients in this sample continued to meet the criteria for major depressive episode at the start of their third week of inpatient hospitalization. Data from a separate questionnaire in this same group (reported elsewhere) suggest that approximately half of the patients with lasting depression acknowledged depressive symptoms that predated their substance abuse. Therefore, it appears likely that this group of adolescents with lasting major depression represent a mixed sample with substance-induced and preexisting autonomous depressive disorders.

The 35% rate of major depressive episode reported here is slightly higher than the figure reported for a similar group of adult inpatients (1) and twice the rate reported for a large group of both inpatient and outpatient adults (3). The 42% rate of conduct disorder reported here is slightly higher than the reported rates of antisocial personality disorder in a comparable adult population (3).

The 21% rate of attention deficit, hyperactivity, or impulse disorder, representing the third most frequent axis I diagnoses in this sample, is notable. The most frequent multiple diagnosis in this sample was attention deficit disorder with hyperactivity plus conduct disorder, paralleling the aggregation of conduct disorder, attention deficit disorder with hyperactivity, and substance abuse diagnoses reported by Gittelman et al. (8).

The 7% rate of phobic or avoidant disorders in this group was surprisingly low, given that the rate of the most similar anxiety syndromes in adult abusers is reportedly much higher, especially among adults who abuse sedatives and stimulants (1, 3).

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Morning Versus Evening Bright Light Treatment of Late Luteal Phase Dysphoric Disorder

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Six women with late luteal phase dysphoric disorder had a significant reduction in depression ratings after treatment with evening, but not morning, bright light. Bright light may offer an alternative to the pharmacologic treatment of premenstrual mood disorders.

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> Truly the light is good, and it is pleasant for the eyes to behold the sun.
>
> —Ecclesiastes 11:7

Bright light has been used to treat seasonal affective disorder (1), seasonal premenstrual syndrome (PMS) (2), and some cases of major depressive disorder (3). Some patients with affective disorders have abnormally phase-advanced circadian rhythms with respect to the sleep-wake cycle (4). Since affective disorders and PMS may be related illnesses (5), we hypothesized that similar circadian phase disturbances also may occur in late luteal phase dysphoric disorder, the *DSM-III-R* category that delineates strict criteria for the condition previously referred to as premenstrual syndrome. Altered levels of estrogen and progesterone may advance and delay circadian rhythms, respectively (6). Patients with late luteal phase dysphoric disorder improve more with a phase advance than a phase delay of their sleep-wake cycle (7), and their minimum nocturnal temperatures tend to be advanced compared to those of control subjects (8). These preliminary findings are consistent with a phase advance disturbance of circadian rhythms in late luteal phase dysphoric disorder. Since evening light can cause phase delay of circadian rhythms while the sleep-wake cycle is held constant (9), we hypothesized that appropriately timed high-intensity bright evening light treatment of patients with late luteal phase dysphoric disorder would synchronize circadian and sleep phases and thereby improve symptoms. Furthermore, we predicted that morning light treatment would cause further desynchronization, exacerbate symptoms, and thus serve as an internal control.

METHOD

The patients were referred from local professionals or were recruited by advertisement. Screening procedures consisted of a structured menstrual assessment questionnaire (adapted from Rubinow et al., NIMH), psychiatric interview, physical examination, and laboratory tests, including chemistry panel, CBC, urinalysis, and measurement of thyroid indices. If the patient had no history of major medical, gynecologic, or psychiatric illness, had regular (26- to 32-day) menstrual cycles, appeared to consistently have affective premenstrual symptoms sufficiently severe to disrupt social or occupational functioning, and was willing to endure the rigors of a long-term research study, she was admitted for a 2- to 3-month diagnostic evaluation.

During the evaluation, patients completed twice-daily mood ratings (100-mm visual analogue scales of depression, anxiety, irritability, fatigue, withdrawal, and global sense of well-being) and visited the clinic weekly for objective (21-item Hamilton Rating Scale for Depression) and subjective (Beck Depression Inventory) depression ratings. To be selected, patients had to meet *DSM-III-R* criteria for late luteal phase dysphoric disorder, have scores of 14 or more on the Hamilton scale and 10 or more on the Beck inventory in the late luteal phase (1 week before the onset of menses), and demonstrate a reduction in scores to 7 or less on the Hamilton scale and 5 or less on the Beck inventory by the week after the cessation of menses. All patients had debilitating affective symptoms that occurred during the late luteal phase of each menstrual cycle throughout the year.

Patients selected for the study then were randomized for 2 months to a crossover trial of morning (6:30 a.m.–8:30 a.m.) versus evening (7:00 p.m.–9:00 p.m.) bright light treatment administered for 7 consecutive days during the symptomatic luteal phase of the menstrual cycle (7–10 days before the onset of menses).

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TABLE 1. Mood Ratings of Six Women With Late Luteal Phase Dysphoric Disorder at Baseline and After Treatment With Morning Light (a.m.) and Evening Bright Light (p.m.)

			Hamilton Depression Scale Score[a]			Beck Depression Score[b]			Atypical Depressive Symptoms Score[c]			Mania Scale Score[d]		
Patient	Age (years)	Marital Status	Baseline	a.m.	p.m.	Baseline	a.m.	p.m.	Baseline	a.m.	p.m.	Baseline	a.m.	p.m.
1	36	Married	27	20	11	20	13	19	11	15	16	1	3	2
2	27	Single	16	11	0	20	11	0	11	10	0	6	1	2
3	32	Married	20	19	6	16	26	3	6	12	7	1	0	0
4	29	Married	22	3	9	16	0	0	18	6	6	1	4	3
5	29	Single	14	5	5	8	0	2	14	0	1	1	7	6
6	31	Married	25	—	11	16	—	—	7	—	6	1	—	0

[a] The group mean±SD baseline, a.m., and p.m. scores were 20.7±5.0, 11.6±7.8, and 7.0±4.2; there was a significant difference between p.m. and baseline scores ($t=9.09$, $df=5$, $p<0.0003$).

[b] The group mean±SD baseline, a.m., and p.m. scores were 16.0±4.4, 10.0±10.8, and 4.8±8.0; there was a significant difference between p.m. and baseline scores ($t=3.87$, $df=4$, $p<0.01$).

[c] The group mean±SD baseline, a.m., and p.m. scores were 11.2±4.4, 8.6±5.8, and 6.0±5.7.

[d] The group mean±SD baseline, a.m., and p.m. scores were 1.8±1.2, 3.0±2.7, and 2.2±1.6.

Menstrual cycle phase was determined by a colorimetric urinary immunoassay for the midcycle luteinizing hormone surge (Ovustick Company). Patients were asked to sit 3 ft from a 2500-lux light source (eight 40-watt, VitaLite fluorescent bulbs or a portable illumination box from Apollo Light), keep their eyes open, and gaze every few minutes at the light. During the month of study, patients were asked to sleep from 10:30 p.m. to 6:30 a.m., take no naps, and to document their sleep times on daily sleep logs. They were also asked to wear goggles to block out light between 6:30 a.m. and 8:30 a.m., when they were being treated with evening light, and between 7:00 p.m. and 9:00 p.m., when they were being treated with morning light, in order to balance the amount of light exposure on both treatment conditions.

At the end of 7 days of light treatment in the luteal phase, mood over the last several days was assessed by two raters, who were blind to the treatment condition, with the Hamilton depression scale, using an addendum to the Hamilton scale that assessed atypical depressive symptoms such as fatigue, social withdrawal, carbohydrate craving, weight gain, and hypersomnia (maximum of 23 points), and with a mania rating scale (Rosenthal et al., unpublished data). The criteria of Terman et al. (unpublished data) were used to determine the response to light treatment: a 50% reduction in scores on the 21-item Hamilton scale, to a score of less than 8. In addition, after each treatment the patients completed the Beck Inventory for Depression.

Patients had been without medication for at least 2 months before the initiation of the study, and all gave written informed consent after the procedures had been fully explained.

RESULTS

Six of the 24 patients screened were selected. Reasons for exclusion included irregular cycles, taking birth control pills, or not meeting diagnostic criteria for late luteal phase dysphoric disorder. The mean age of the subjects was 30 years (range, 27–36), and most of them had suffered from this disorder for more than 5 years. Four of the six women were employed outside the home.

During the evaluation, the mean±SD Hamilton ratings, reflecting symptoms during the *previous* week, were as follows: week 1 (cycle days 1–7), 11.6±9.7; week 2 (cycle days 8–14), 7.6±7.2; week 3 (cycle days 15–22), 10.7±6.4; and week 4 (one week before the onset of menses), 20.0±4.2. The mean±SD Beck ratings were as follows: week 1, 7.5±8.3; week 2, 3.0±4.7; week 3, 7.4±4.7; and week 4, 15.6±3.5.

One patient (table 1, patient 6) did not complete the morning light treatment because of her spouse's objection. Patient 4, who developed severe agitation after 2 days of receiving 2 hours of morning light, used only 1 hour of morning light the remainder of the week. During the treatment phase of the study, all the ratings done during the late luteal phase were obtained before the onset of the next menses.

Analysis of variance revealed significant treatment effects for Hamilton depression ratings ($F=16.10$, $df=2, 9$, $p<0.001$). Beck depression ratings approached significance ($F=3.25$, $df=2, 8$, $p\leq0.09$). Post hoc t tests revealed that, compared to baseline (the mean ratings obtained during the late luteal phase in the months before light treatment), there were significant reductions in Hamilton and Beck depression ratings after evening light treatment. After morning light treatment, there were no statistically significant differences from baseline in Hamilton ($t=0.63$, $df=4$) or Beck ($t=1.25$, $df=4$) ratings.

The differences between morning and evening light on Hamilton ($t=1.49$, $df=4$) and Beck ($t=1.4$, $df=4$) depression ratings did not reach statistical significance. In addition, delta change scores from baseline were not statistically significant between morning and evening light treatments. Mania scores were low throughout the study and, like the atypical depression ratings, did not vary significantly. There were no significant order effects as a function of which light treatment was administered first.

DISCUSSION

One week of daily, 2-hour, evening light treatments significantly reduced Hamilton depression ratings in patients with late luteal phase dysphoric disorder. The response to evening light is consistent with the hypothesis of a phase advance of circadian rhythms in this disorder. The benefits of morning light, while not significant, showed a favorable trend. That morning light did not exacerbate symptoms and was not significantly different from evening light suggests that the effects of light may not be mediated entirely through shifting circadian phase (10) and that in this disorder, morning light cannot serve as an internal control.

Further trials with a larger number of patients and with an additional placebo control condition are warranted. Nonetheless, these initial results are promising and suggest that bright light may serve as an alternative to the pharmacologic management of late luteal phase dysphoric disorder.

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Calcium Channel Blockers for Tardive Dyskinesia in Geriatric Psychiatric Patients

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Nifedipine treatment resulted in variable improvement in tardive dyskinesia in eight geriatric psychiatric patients. Patients with affective disorders and hypertension demonstrated improvement in other areas as well.

(Am J Psychiatry 1989; 146:1218–1219)

In addition to an established role in the treatment of essential hypertension, calcium channel blockers have shown efficacy in various other disorders including acute mania (1) and tardive dyskinesia (2, 3). Of all age groups, the geriatric population has the highest prevalence of both cardiovascular disorders and psychopathology, as well as tardive dyskinesia (4); at times the three disorders appear simultaneously in the same patient. We report herein calcium channel blocker treatment of geriatric psychiatric patients for combined hypertension and tardive dyskinesia or tardive dyskinesia alone.

METHOD

Eight geriatric psychiatric patients (ages 77–86) all suffered from persistent tardive dyskinesia, as defined by accepted standards (5), of at least 15 months' duration. Three patients also had essential hypertension (table 1, patients 2, 5, and 8). In each case, tardive dyskinesia had developed during continuous neuroleptic use over several years and consisted of buccolabial-masticatory and/or limb movements. The condition remained unchanged with time or with subsequent reduction of neuroleptic dose. Within 2 to 3 months on a regimen of a reduced dose of neuroleptic, however, all eight patients demonstrated worsening of psychopathology, which again improved with a higher dose. For at least 5 months before and during the trials of calcium channel blockers, there were no further medication changes in any patient. Other long-term medications used by the patients included clonazepam (patients 2, 3, and 6), nonsteroidal anti-inflammatory drug (patients 2 and 5), and lithium carbonate (patient 8).

Each patient gave informed consent to try a calcium channel blocker for dyskinetic movements and, if applicable, hypertension. Each further agreed that this treatment would be discontinued on request or at the doctor's discretion. Dose was tapered upward until tolerance or maximum improvement in score on the Abnormal Involuntary Movement Scale was reached. Blood pressure was recorded daily for 2 weeks after each increase in dose and once weekly thereafter; ECG was taken biweekly. Treatment with diltiazem, a relatively short-acting calcium channel blocker, was initially started in three patients (patients 2, 3, and 7) but was replaced by treatment with prolonged-action nifedipine, which was then used by all eight patients.

RESULTS AND DISCUSSION

In the three diltiazem-treated patients, an initial antidyskinetic effect wore off within 1 to 3 months. Limited duration of efficacy has been noted previously for diltiazem used in this context (6).

The effects of nifedipine are summarized in table 1. All eight patients achieved substantial initial improvement in dyskinetic movements, but three could not tolerate hypotensive effects and nifedipine was withdrawn. In the remaining five, diastolic blood pressure fell an average of 10–15 mm Hg without untoward effect. There were no significant ECG changes. Overall improvement in tardive dyskinesia was sustained from 4 to 8 months. Nifedipine was withdrawn from the two schizophrenic patients after 5 and 8 months, respectively, because of worsening hostility, a phenomenon reported previously in schizophrenic patients taking this class of medication (7). In all five patients in whom nifedipine was discontinued, tardive dyskinesia returned to baseline levels within 10 days to 6 weeks of discontinuation, which suggests a carryover effect. Previous reports on shorter-acting calcium channel blockers have noted sudden relapse on discontinuation of treatment.

In the remaining three patients—two with bipolar

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TABLE 1. Effects of Prolonged-Action Nifedipine on Tardive Dyskinesia, Hypertension, and Mood in Eight Geriatric Psychiatric Patients

						AIMS Score[a]			Blood Pressure (mm Hg)		
Patient	Sex	Age (years)	Diagnosis	Maximum Dose of Nifedipine	Length of Treatment (months)	Pretrial	At Maximum Dose	End of Treatment	Pretrial	End of Treatment	Mood Change
1	F	77	Schizophrenia	40 mg, b.i.d.	8[b]	13	4	6	140/85	130/70	Increased hostility
2	F	83	Bipolar	40 mg, every morning 20 mg, every evening	4	18	9	8	160/95	140/80	Decreased irritability
3	F	86	Bipolar	20 mg, b.i.d.	2[c]	11	6	8	130/85	110/60	
4	F	80	Schizophrenia	40 mg, every morning 20 mg, every evening	5[b]	14	5	6	140/80	120/70	Increased hostility
5	F	82	Bipolar	20 mg, b.i.d.	5	9	4	4	160/100	130/90	Decreased irritability
6	M	80	Bipolar	40 mg, b.i.d.	2[c]	8	3	5	130/80	95/55	
7	M	85	Bipolar	20 mg, every morning	1[c]	20	10	10	125/85	90/55	
8	F	85	Schizoaffective	40 mg, b.i.d.	4	10	2	2	170/100	145/85	Decreased irritability

[a] Maximum score=28.
[b] Discontinued due to hostility.
[c] Discontinued due to hypotension.

and one with schizoaffective disorder—the following pattern emerged: effective control of hypertension, marked improvement in alertness and sociability, decrease in chronic irritability, and sustained improvement in tardive dyskinesia. It was unclear whether the affective changes reflected improved comfort or self-image or involved a possible effect of calcium channel blockade on pathophysiology common to other disorders as well. In any event, mood-altering properties have been described for various drugs of this class. Verapamil may have antimanic potential (1). It has long been recognized that pimozide, a neuroleptic which combines potent calcium channel blocker activity with highly selective dopamine receptor blockade, improves negative symptoms in chronic schizophrenia (8) and may do the same in chronic dementia (9).

However, without a controlled study, no conclusions regarding the efficacy of calcium channel blockers for tardive dyskinesia can be drawn. For the elderly, in particular, the currently available calcium channel blockers cannot be endorsed as safe treatment for tardive dyskinesia, given the risk of serious hypotension, diminished cerebral perfusion, and potential for relapse. However, in cases of geriatric hypertension or other appropriate cardiovascular indications, as well as tardive dyskinesia, judicious use of a calcium channel blocker may be considered. Caution should be taken because of potential toxic interactions with other drugs such as lithium and other antihypertensives including beta blockers. Nevertheless, even transient and limited relief from severe dyskinetic movements would be highly appreciated by geriatric patients with these disorders, their families, and care givers. The development of newer calcium channel blockers with exclusive CNS activity may enhance our understanding and treatment of psychopathology and neurological consequences in the elderly.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

SOMATIC THERAPIES

Drugs and Behavior: Cause, Effects, and Treatment, *by Bernard Segal, Ph.D., with Don Cahalan, Ph.D., consulting editor. New York, Gardner Press, 1988, 444 pp., $39.95.*

This is generally a good book. It is well written and well organized. Dr. Segal communicates his material clearly and in a fashion that is naturally enjoyable to read. Although somewhat lacking in new material, this book is an excellent accumulation of information.

The organization of the book is good and allows for easy access to specific information without having to read unnecessary material. This is further facilitated by an excellent index. The book is divided into 16 chapters, each devoted to a particular kind of drug-related behavior. The first 60 pages or so deal primarily with social issues, basic terminology, and an introduction to the properties of psychoactive drugs. In this early part of the book, concepts of tolerance, dependence, and drug-seeking behavior are discussed and a historical perspective of the social and political influence of drug use is provided.

The next 100 or so pages give a very reasonable review of the physiological mechanisms of action for common psychoactive agents. The approach to psychopharmacology is straightforward and accurate but not quite detailed enough for the requirements of an experimental psychopharmacologist. The following chapters deal well with various aspects of drug use, including theories of chemical dependency, psychological perspectives on drug-seeking behavior, and approaches to treatment. I was pleased to see that this book discusses the financial effects of alcohol abuse as well as the physical and psychological complications. It is also noteworthy that a chapter concerning tobacco use is included. Although this topic is only briefly covered, it is well handled and the chapter is an excellent contribution.

The chapters on alcoholism are particularly good. The book devotes approximately 100 pages to the topic of alcohol abuse and they are used quite effectively. Considerable time is spent discussing the effects of alcohol on physical health as well as its social impact. The concept of alcoholism as a disease is well handled, and alternatives to the disease concept are also discussed. Multidimensional concepts of drinking-related behavior and associated problems are also discussed. There is also a good chapter on alcoholism treatment that describes a variety of modalities.

This book also has a chapter on prevention of drug-related problems. Since this is an often neglected topic, it was refreshing to see it mentioned.

The primary problem with this book is that it tries to cover too many topics. It is hard to imagine that the broad area of drugs and behavior could easily be condensed into fewer than 500 pages. It would have been nice to see more information on each topic and more emphasis on current research findings. *Drugs and Behavior* is, however, an excellent reference book for someone interested in substance abuse treatment. It is inclusive and enjoyable to read, managing to deal with pertinent topics without needless jargon and without becoming verbose. It provides interesting material on the area of drugs and behavior with a view toward substance abuse treatment.

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Electroconvulsive Therapy, *by Richard Abrams, M.D. New York, Oxford University Press, 1988, 222 pp., $29.95.*

In this era of procedure-oriented medicine, ECT provides an important undertaking in psychiatric medical management. In this single volume Dr. Abrams brings us up-to-date on ECT, a sophisticated procedure that many nonphysicians as well as colleagues in other medical fields felt went out with the Dark Ages. Dr. Abrams shows that this procedure is one of the safest, not only in psychiatry but in anesthesia and medicine as well, for the treatment of patients who are refractory to medication, patients for whom the use of various psychotropic drugs is contraindicated, or patients in emergency need of reversal of a psychiatric condition. The foreword to this volume is provided by Dr. Max Fink, which is fitting because his volume (1), dated a decade ago, is the quintessential predecessor to this well-written book on a very controversial subject.

One of the greatest advantages of this book is that it is written by a single author who has extensive experience in the area of modern ECT. This allows for a great continuity from beginning to end. Dr. Abrams leads the reader into this volume with a brief historical review that not only stimulates interest but also provides a perspective for the beliefs that are held by patients and families when first confronted with the possibility of choosing ECT as a viable therapeutic option in the treatment of various mental dysfunctions. Movies such as *One Flew Over the Cuckoo's Nest* have done little to change the public's negative image of this procedure. (It is interesting to note that the movie was set in 1965, the year a new age of ECT began with the use of modern anesthetic agents.) Preconceived negative notions about ECT account for the apparently defensive nature and tone of this volume.

Dr. Abrams does a fabulous job of covering medical evaluation, basic reviews of anesthetic agents, principles of electricity, and cerebral pathology. In describing the technique of ECT, he does a superb job of explaining the various phases of the therapy and the various patient considerations, which makes this an excellent clinical manual. At the end of this particular chapter Dr. Abrams presents a stepwise guide for the administration of ECT that nicely consolidates the principles and theory behind this procedure.

The concluding chapter of the book deals with patients' attitudes and legal considerations. Finally, there is an excellent, up-to-date list of the references that have been cited throughout the text. This compact presentation of the literature makes up for the awkward footnoting in the body of the text and should be very useful to those with a professional interest in ECT.

A lack of illustrations and a lack of graphic presentations of data make for some reading that may be worse than the dry mouth patients complain of with the use of atropine as a pre-ECT medication. Because of the past abuses of electric therapies, misinformation, and our society's valuation of memory, the author gives over what seems to me a disproportionate amount of space in a volume of this size to the memory and cognitive functioning of individuals after ECT.

In his discussion of the training requirements for administering ECT, Dr. Abrams offers some guidance but fails to highlight the importance of learning about advanced cardiac life support, but this may be outside the realm of this volume. He also stresses only unilateral treatment, which is unfortunate in view of the fact that some professionals and institutions prefer and use bilateral ECT almost exclusively.

This book should be mandatory reading for any individual who has an active part in the evaluation, administration, or care of patients undergoing ECT. It should be made available to all patients and family members who are asked to consent to the procedure, but this should not replace the physician's responsibility for adequately explaining the procedure to these individuals.

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Handbook of Clinical Psychopharmacology, 2nd ed., *edited by Joe P. Tupin, M.D., Richard I. Shader, M.D., and David S. Harnett, M.D. Northvale, N.J., Jason Aronson, 1988, 465 pp., $50.00.*

The editors of this volume are in an excellent position to compile and critically review the most current information about clinical psychopharmacology because of their own expertise and ongoing collaboration with the large group of clinicians and psychopharmacologists who participate in the annual psychopharmacology workshop at the Tufts-New England Medical Center. This second edition of the *Handbook of Clinical Psychopharmacology* represents the editors' successful effort to address the most frequently asked questions about the subject and to distill the ever-widening body of clinical psychopharmacology research into a concise, usable, and well-referenced collection of clinically oriented chapters.

The first chapter is an excellent discussion of the use of antipsychotic medications and the clinical syndromes in which psychotic symptoms may occur. Chapter two reviews the diagnosis and medical differential diagnosis of major depression, plus the principles of treatment in drug-responsive and drug-resistant patients. Working definitions of stress, fear, and anxiety, along with a discussion of some *DSM-III* anxiety disorders, plus options for their psychopharmacological treatment are well presented in chapter three. Acute and maintenance treatment of the patient with mania or secondary mania and pharmacological management of rapid cycling patients are concisely reviewed in chapter four. Chapter five is a relevant but brief focus on psychopharmacology as it relates to the origin and treatment of violence. The outline of diagnostic and treatment issues is a helpful introduction to this area. In spite of the omission of any discussion of nicotine addiction in the next chapter, which concerns substance abuse, the in-depth consideration of pharmacological approaches to the treatment of opiate, barbiturate, and alcohol withdrawal, plus alcoholism, alcoholic hallucinosis, and psychostimulant abuse, will be exceedingly helpful for many readers.

Chapter seven, "Memory Disturbance and Cognitive Impairment in the Elderly," is a scholarly review of delirium, dementia, amnestic syndromes, Alzheimer's disease, and dementia accompanied by depression, paranoia, anxiety, or agitation. One ambiguous statement on page 170 appears to suggest that anterograde amnesia is characterized by an ability to learn new material. Guidelines and specific recommendations for the use of drug therapy in childhood and adolescence are carefully and extensively reviewed in chapter eight. Chapter nine is a clear, concise, and authoritative review of psychopharmacological approaches in the treatment of anorexia nervosa and bulimia. Chapter ten, "Treatment-Resistant Problems," is an excellent discussion of potentially confounding treatment variables in primary and secondary affective illness and schizophrenia.

Chapter 11 successfully clarifies the potentially confusing literature on the origin, diagnosis, and treatment of atypical depression and ends with helpful practical considerations. Attention deficit disorder, residual type, or adult hyperactivity is discussed in chapter 12, which provides diagnostic and treatment guidelines for this important syndrome. Chapter 13 contains an essential discussion of drug combinations and interactions. As an index of the completeness of this chapter, the infrequently referenced and potentially fatal interaction between antidepressants and the coumarin type anticoagulants (1) is clearly indicated in this material. Omission of references from the body of the tables in this chapter, however, may deter the reader inclined to pursue more information.

Chapter 14, a discussion of the relationship between psychotherapy and psychopharmacology, is an informative, well-referenced consideration of the literature relevant to the treatment of schizophrenia, affective disorders, and some anxiety disorders. Chapter 15 is a short, helpful review of the use of serum drug concentration monitoring. A few clinical examples pertinent to this potentially complex area would be a welcome addition.

One begins chapter 16, on liability issues and malpractice prevention, with a sense of dread. Nevertheless, after reading this chapter one feels more prepared, grateful for the information, and wanting more to read. The final chapter, a glossary of psychopharmacological terms that includes such items as Scatchard plot, will be a useful reference for those who wish to dig into the psychopharmacology research literature.

This volume is an indispensable resource for all mental health clinicians and allied professionals whose area of focus is in any manner related to the treatment of individuals with psychiatric illness. In addition to being a superior clinical reference text, it is highly palatable and may be read from cover to cover by those eager to learn about selected topics in psychopathology and clinical psychopharmacology.

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BRAIN IMAGING

Brain Imaging: Applications in Psychiatry, *edited by Nancy C. Andreasen, M.D., Ph.D. Washington, D.C., American Psychiatric Press, 1989, 370 pp., $75.00.*

This volume is an ambitious undertaking; the editor is to be congratulated for bringing together all of the major imaging techniques now available except for the curious omission of a chapter on regional cerebral blood flow, which is referred to by several of the authors and is widely used.

Dr. Andreasen has deliberately chosen to have each chapter written independent of the others. Her goal has been to allow a reader interested in one technique to be able to study it in depth. Therein lies the strength and the weakness of this book. The reader who wishes to review the total spectrum of imaging is faced with considerable duplication. Some of the same subjects are mentioned in several chapters. The differing views and personal opinions of the authors can be confusing and sometimes are bewildering. The topic of tomographic reconstruction is common to four of the five chapters and might have been more efficiently covered in a single chapter. Principles of radiology and nuclear medicine are common to three of the five chapters and might also have been better covered in one chapter.

The attempt to divide each chapter into an introduction and technical section and then to present clinical material and possible applications is laudable. As might be expected, there is an unevenness to this approach. In spite of this caveat, however, the book is an update and major improvement over anything previously written on this subject.

Jeffrey A. Coffman's chapter on computerized tomography (CT) in psychiatry begins with an excellent historical review. Artifacts are not illustrated, however. This is especially bothersome because almost all artifacts are described as streaking. No distinction is made between artifacts of a cosmetic nature and those actually distorting data. Clinical studies are extensively reviewed with some attempt at integration. Perhaps a weakness is the omission of the neuropathological literature. If CT suggests tissue loss, this should be checked postmortem by actual measurements of wet or dry weight. This integration is particularly absent for groups with affective disorder. Also, the lack of specificity (i.e., ventricular and sulcal widening being present in all psychiatric conditions) is insufficiently addressed. Nevertheless, this chapter provides a good discussion of the diagnostic utility and cost-benefit ratio of CT. This information is particularly welcome in the light of the paucity of literature on these subjects.

Dr. Andreasen's chapter on nuclear magnetic resonance imaging (NMR), or magnetic resonance imaging (MRI) as it is now more commonly referred to because of the pejorative connotations of the word "nuclear," is richly illustrated and provides the best explanation of MRI principles ever published. This chapter should be of inestimable value to the psychiatrist. There are some minor errors, more of a typographical nature, such as on page 70 where higher fields are claimed to reduce the signal-to-noise ratio instead of enhancing it, but this does not detract from its usefulness. Whether researchers can design their own scanning sequences is debatable. This excellent chapter might have been further strengthened by comparisons of CT and MRI (e.g., have all CT claims been replicated by MRI?). The potential of spectroscopy may be severely underestimated, but at present this is a matter of opinion. More about lactate metabolism in panic disorders would have been most welcome.

John M. Morihisa's chapter on computerized EEG and evoked potential mapping omits a discussion of underlying physical principles but devotes much time to technical detail (e.g., Grass 7P511 EEG amplifiers). The author seems to be referring to the Duffy and Coppola systems as two different "techniques" that exhaust the field. Actually, they are two commercial implementations, differing in slight detail, among 20 other commercially available systems. Mention of the work of Roy John and his group at New York University as well as the methodological techniques of Gevins and Donchin would have helped give perspective to this presentation.

The chapter by Michael D. Devous, Sr., on imaging brain function by single-photon emission CT is flawed by several errors. On page 148, autoregulation is mistaken for metabolic coupling. On page 153, nonparallel beams are not reflected; they are absorbed. Also, on pages 153 through 155, he repeatedly refers to single-photon emission CT, including detector systems and rotating gamma cameras, without distinction. On page 155, he states that any plane, not just the transverse plane, can be acquired and reconstructed. This ignores the difference between acquired data and secondary image processing and extrapolation. Most researchers would disagree that one must apply a mathematical model to diffusible indicators, as stated on page 167. These statements are not as important to the clinician as they are to scientists doing research with single-photon emission CT, but clinicians could seriously question Dr. Devous's comment on page 176 that neither single-photon emission CT nor positron emission tomography (PET) can be used diagnostically in individual patients unless a severe structural abnormality such as stroke or tumor is also present.

The review of technical issues is limited to the author's own work, which does not give us a broad overview of the field. The review of research and clinical applications involves regional cerebral blood flow and PET more than it does single-photon emission CT. Dr. Devous expresses considerable enthusiasm for his own group's studies of schizophrenia and affective disorders. The work suffers, however, from a lack of quantitative data. Presentation of group results rather than case reports alone would have been more helpful. Finally, the review of findings in dementia is oddly unrepresentative. Most of the literature cited is old and not up-to-date. Some newer literature is cited but with glaring omissions. Neuropathological validation from the work of Risberg and Gustafson is a prime example.

Henry H. Holcomb, Jonathan Links, Caroline Smith, and Dean Wong complete the volume with an in-depth examination of PET. The discussion is far too detailed for a general audience (the 2-deoxy-D-glucose and oxygen-15 models, for example) and contains some errors such as confusing concentrations and quantities, but these authors present a thorough review of experimental design and methodology. The review of clinical research findings is particularly good, as is the integrative summary for each condition. Their statement that there is hypometabolism in the temporal, frontal, and parietal regions in Alzheimer's disease might lead one to conclude that Alzheimer's disease is visible as a virtually total reduction of brain metabolism. It is equally untrue that depression is visualized as a right temporal hypometabolism (p. 239). The section on costs and practical requirements is very good. Quoting the cost of a top-of-the-line cyclotron at $1.65 million, however, is far too optimistic and unrealistic with the rapid escalation in costs of these expensive instruments.

In spite of some shortcomings, this is a valuable and indispensable book. For psychiatrists interested in brain imaging, this volume is mandatory reading. It is the only work ever to attempt the interface between psychiatry and imaging. It contains almost all the information about imaging that any interested reader might need.

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FAMILY THERAPY

Marital and Family Therapy, 3rd ed., *edited by Ira D. Glick, M.D., John F. Clarkin, Ph.D., and David R. Kessler, M.D. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich), 1987, 595 pp., $39.50.*

For psychiatric residents and more senior psychiatrists who are not experienced in marital and family therapy, the third edition of this textbook should fill a substantial void in their psychiatric education. (Other introductory texts on family therapy are primarily oriented toward persons who expect to develop professional identities as family therapists.) This book will help such readers obtain an overview of the broadened scope and applicability of family approaches. In addition, it will serve a distinctive bridging function by conveying principles and guidelines useful for mental health professionals whose primary identity is not as family therapists.

The substantial changes from earlier editions (1974 and 1980) reflect the expanded contexts in which couples and families are now being seen. These changes also provide a more comprehensive integration of current concepts and methods of family assessment and treatment. The complexity of the field of family therapy now calls for 35 chapters divided into 10 sections.

Unlike most other family therapy texts, major attention is given to family evaluation and treatment when one family member has a diagnosable psychiatric disorder defined in *DSM-III-R* terms. Explicit attention is also given to other major psychiatric problems that do not readily fit the format of individual psychiatric disorders—problems of domestic violence, incest, the impact of potential suicide and acute or chronic illness on other family members, and integration of family intervention with hospital programs and health disciplines such as medicine, surgery, and rehabilitation.

Special attention is also given in this edition to the relevance for treatment of variations associated with nontraditional forms of family life, for example, single-parent families, remarried families, dual-career families, and gay couples. The editors also include other topics well beyond the scope of usual introductory textbooks. For example, they have extensive chapters on research on the outcome of processes of family therapy, training issues in family intervention, and ethical, financial, and professional issues in family therapy.

This book covers an extraordinary amount of ground on the current state of the art in family intervention. However, the editors explicitly recognize both the limits and the potentialities of family concepts and methods. They state in their preface,

> The field has gone beyond its heyday of enthusiasm and advocacy of family intervention for every clinical condition, to a more sophisticated (and sober) time of differentiation. This differentiation is taking place on many levels . . . [when] family therapy is indicated, and when it is not helpful; when the symptoms are under systems control and when they are more strongly determined by other factors, such as biological ones; how one evaluates in order to make *both* individual diagnoses and a family "diagnosis"; when the whole family is the patient and when the family is serving as co-therapist to help the individual with symptoms; when behavioral strategies of family intervention are more useful than systems strategies. (p. xxviii).

Having "opted to take the route of maximum breadth," the editors acknowledge that they necessarily present some topics too briefly to satisfy experienced family therapists. This may be especially true for the mere 10 pages given over to descriptions of the major schools of family therapy, collapsed into four constellations. Most other family texts are exclusively devoted to the viewpoint of a single school or to detailed comparisons of major schools, but Drs. Glick, Clarkin, and Kessler attempt to delineate principles that apply across schools. For those who want to pursue a subject in greater depth, briefly annotated references are supplied after each chapter. Experienced therapists will inevitably find topics for which they would have chosen different references or viewpoints. However, the individual authors commendably take clear-cut stands on current, controversial issues. They do so with lucid, meticulous attention to currently available evidence. The result is balanced yet forthright, comprehensive yet selective, and specialized yet comprehensible.

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Divorce as a Developmental Process, *edited by Judith H. Gold, M.D., F.R.C.P.(C.). Washington, D.C., American Psychiatric Press, 1988, 166 pp., $19.95.*

It was with a sense of enthusiastic expectation that I purchased this book while browsing through the American Psychiatric Press bookstore at the APA annual meeting in Montreal in 1988. It seemed that finally someone had put together a book about divorce as part of adult development—a moving on in life. I relished the idea of reading something positive about divorce or at least something about the possibility of divorce having long-term positive sequelae. When I got a second copy of the book from the *Journal* with a request to review it, I felt doubly blessed. Not only did I have a second copy to give to a colleague, but now I was forced to take my copy off my "to do" stack and read it. To my great surprise, when I finished the book I felt disappointed.

Edited books often suffer from a heterogeneity of themes, styles, and value of contributions. This collection suffers seriously from this problem. It is a rare achievement when an edited volume contains well-written chapters of comparative value, all closely related to a continuously developing subject. This book's main difficulty, however, lies in the relationship of its title to its contents and its view of the causes and outcome of divorce.

Divorce as a Developmental Process is about many things, but it is not about divorce as a developmental process. I am not sure it is fair to say that the book is really about divorce. In truth, it is about divorce as experienced by certain women. "Assessing and Treating Divorcing Men" and "The Impact of Parental Divorce on Children and Adolescents," by Michael F. Myers and Elissa P. Benedek, respectively, stand out as well-written separate works generally unrelated to the volume as a whole. R. James Williams's chapter on the legal aspects of divorce is an attempt to help lawyers understand the human feelings stirred up in their clients by divorce. It pleads for control of the excessive damage the legal profession can do to the divorcing couple and their children and clearly addresses a separate audience from that addressed by the rest of the book, which seems written for mental health professionals.

The five remaining chapters are all more or less devoted to one theme and would make a fascinating, more coherent book. These chapters address divorce from the perspective of women, with an emphasis on feminist attitudes and ideas.

Beginning immediately in chapter one, the reader gets a strong sense of bias in the author's view of divorce. Leah J. Dickstein portrays men as narrow-minded, selfish, thoughtless creatures who are emotionally unresponsive to their more insightful wives—women who have a yearning to grow and mature as mothers and people but who are thwarted by their domineering, inhibited husbands. Divorce for women thus becomes a necessary but painful act of self-liberation. From the first sentence of this chapter, which mentions Betty Friedan and the National Organization for Women, to the conclusion, which suggests that therapists be aware of their sexist attitudes (against women, not men), it is clear that the author represents an extreme "feminist" position regarding divorce.

In "Belittling: Psychosocial and Legal Considerations," the editor, Judith Gold, and Edgar Gold continue to present essentially a woman's perspective. Rather than writing about how troubled spouses denigrate each other, these authors define "belittling" as what men do to their wives when they are threatened by their wives' assertiveness or maturation. The authors conclude that "the adversarial nature of the divorce, custody, and property settlement process will . . . ensure that the husband's bitterness, which was the root cause of the belittling process, is perpetuated through the divorce proceedings" (p. 44). This chapter ignores the fact that the belittling process is not gender specific and can take place in both directions in troubled marriages.

Martha Kirkpatrick's chapter, "Some Clinical Perceptions of Middle-Aged Divorcing Women," is a well-written, straightforward, appropriately titled social commentary on the struggles of such women. It pulls no punches and states its case fairly from the feminist perspective: "Middle-aged women who have been part of the married world for many years are unaware that this world is chauvinistic, elitist, and highly ritualized around the existence of a husband" (p. 96).

In the book's summary chapter, "Divorce as Development: The Process of Psychotherapy," Judith Gold once again returns to the central theme of the book—her feminist perspective on the effect of divorce on women. Although men are mentioned, they are usually cast as villains. As an example, the custodial parent (always referred to as "she") is the only one mentioned who worries about the effects that the custody fight will have on the children involved. Gold points out that husbands often refuse to attend marital therapy or mediation sessions. In my own practice, I have found that although some men are harder to engage in marital therapy, women are also often unwilling to engage in mediation in the midst of severe divorce pathology.

Divorce as a Developmental Process is correct in pointing out that divorce has become more prevalent since World War II due to changes in gender role expectations, but it relatively neglects other reasons for divorce and the problems couples face before, during, and after marital separation. Disturbed marriages have been with us forever. Divorce is fundamentally caused by unsatisfying marriages that, in turn, are caused by a myriad of etiological factors. The feminist revolution is undoubtedly partly responsible for making divorce a more viable option for unhappily married men and women, but the change in gender roles in our society is only one of many factors involved in the increasing frequency of divorce. It may not be the most important, only the latest.

This book should be subtitled *A Feminist Position*. It is essentially a feminist vision of divorce. It does not give enough credit to either men or women for getting through a terrible period of their lives and doing better on the other side of it. It emphasizes the sociological, not the psychological. It mostly blames men for divorce and its sequelae and sympathizes with women. I personally have found a less stringent feminist position critical in working with divorcing men and women. Such a position allows for greater sensitivity to the similarities and differences between men and women. It supports adult development of both sexes—independently and together. It promotes fair and reasonable, nonadversarial divorce and custody laws. Mental health professionals who want to help divorcing couples must recognize the social pressures on both men and women and must be equally cognizant of the emotional problems of both sexes. Some women, however, will sympathize with the strong feminist perspective presented in some chapters of this book. It clearly demonstrates and indirectly cautions that therapists working with divorcing men, women, or couples are working with clients who are likely to bring to the therapist many different and intense attitudes, feelings, and conceptions that will shape the healing process.

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PSYCHOANALYSIS AND PSYCHOTHERAPY

Masochism: Current Psychoanalytic Perspectives, *edited by Robert A. Glick and Donald I. Meyers. Hillsdale, N.J., Analytic Press, 1988, 238 pp., $29.95.*

This book is about a daunting and disappointing area of clinical practice, about some of the most difficult challenges faced by a psychoanalytically oriented therapist. It is hard enough to bear witness to the stories of cruelty, humiliation, and degradation experienced by our patients at the hands of others; normal human empathy alone makes us partner to their pain. When we learn that a patient not only fails to avoid such situations but seems to seek them out with avidity, we must overcome our own innate revulsion and the consequent tendency to distance ourselves and reject whoever has become the source of our discomfort. Books like this help immeasurably because they teach us that we share this discomfort with the best among us.

The editors, members of the Columbia University Center for Psychoanalytic Training and Research, asked members of their own group (and a couple of their friends outside) to survey the spectrum of clinical masochism. Liebert's review of the psychoanalytic concept of character leads naturally to subsequent chapters on the sources of excitement in sadomasochism (by Coen), the inability to tolerate success (by Schafer), repetition compulsion (by Gedo), and the inevitable component of narcissism bundled in during the developmental process (by Cooper). There are papers on the precursors of masochism, detected by some theorists during infancy, childhood, and adolescence.

Two papers stand out. Otto Kernberg's tightly written summary of the clinical dimensions of masochism presents the results of his own careful investigations as well as a useful set of criteria by which to judge the degree of severity of masochistic illness. Kernberg takes care to describe Fairbairn's approach with great clarity and points out that different theoretical systems offer different modes of understanding. Throughout his paper one can see the logic behind most forms of transference and countertransference distortion experienced during treatment. In the other outstanding chapter, Helen Meyers explains her concept of treatment in terms so clear and logical that one is able to review one's own cases to see where they fit in her system. Such papers as Kernberg's and Meyers's are rare enough in any book, and they shine brightly in this one.

Despite the overall high quality of the book, it has some central flaws. Contemporary psychoanalysis is too pluralistic for a presentation by the members of any one local society; these authors are more parochial than they can recognize. Too many of the patients discussed were only mildly impaired by their illness. Although some may claim that the success of treatment with such patients implies that more severely ill patients might prosper similarly, the knowledgeable reader longs for a presentation by one of those known for their interest in the terribly ill, like Stoller or Wurmser.

Another flaw is inherent in the basic concept behind the book—psychoanalytic investigation may provide only a recursive validation of classical drive theory rather than assist the search for new ways of understanding and new modes of treatment. Several authors in this book even revive Freud's early idea of a masochistic drive, as if we were still in an era when the unknown or the otherwise inexplicable might be elucidated by a hypothesized untestable force. The absence of chapters by a self psychologist, a cognitive therapist, or a behaviorist may seem only natural to the editors, but it reduces the value of an otherwise good collection.

Written by the editors, the introduction is at once the most comprehensive, the most important, and the most difficult chapter in the book. No one who can understand it on first reading needs the book. I recommend it as a test to be read after working through the whole volume.

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Freud, Women, and Morality: The Psychology of Good and Evil, *by Eli Sagan. New York, Basic Books, 1988, 288 pp., $19.95; $9.95 (paper).*

This book contains five sections, each interdependent with the others: Conscience and Super Ego, Morality in History, The Psychoanalytic Theory of Morality—A Critique, Toward a Reconstruction of the Psychoanalytic Theory of Morality, and Conclusion: Time Present, Time Future. These headings give a preliminary idea of the book's contents, perhaps more accurately than does the book's title.

I will give a brief review of the theories presented by the author. Sagan presents the argument that the conscience and the superego are not the same structure but that conscience influences and directs the superego. He places Freud's theories within the cultural context of Vienna and the bourgeoisie of the era and points out contradictions and ambivalent thoughts in Freud's writings. I enjoyed Sagan's use of Huckleberry Finn's moral dilemma about his friend the escaped slave to illustrate the role of conscience in battling the more socially determined force of the superego. Sagan discusses the ability of Nazi doctors to be both physicians and murderers by describing the formation of the superego through cultural and social teachings of what is for the good of all without having an infusion of love and of conscience. He tells us that only conscience can judge the superego and tell what is moral or immoral:

> Whereas Freud asserted that the superego, after its formation, subsumed the functions of the ego ideal, conscience and self-observation, it may be more accurate to say that only conscience, using the capacities of idealization and self-observation, has the capacity to judge the superego. Only conscience can tell us what is moral or immoral, only conscience can discriminate between the beneficial and corrupt aspects of the superego. It is conscience, not superego, that enables a person to behave more morally than his or her parents and provides the capacity for society to make moral progress. (pp. 20–21)

The next section deals with history and an exposition of how slavery could be justified in one era and not in another. From here Sagan takes us to the period 1600–1800 and changing attitudes toward child rearing as well as the initial rise of feminism as women first demanded equality. This leads Sagan to his next point, that men fear sexuality, their own and that of women. It is this fear which refuses equality. He proposes that throughout modern history there is a distinct ambivalence, that as men allow greater freedom for other men—through the abolition of slavery, colonialism, and huge economic disparities—their treatment of women and children becomes harsher and restricted. "Masculine exercise of dominion over other men is by no means unrelated to deep unconscious struggles, rages, and anxieties concerning women" (p. 33).

According to Sagan,

> This book was written for a larger purpose: To demonstrate that Freud's anxiety about women produced not only antifeminist theory on matters directly concerning women but also crucially important theoretical distortions in areas that, on the surface, do not bear directly on the question of male-female equality. It will be argued that as a result of the hidden antifeminine bias the psychoanalytic theory of morality is inadequate. Similar distortions of the truth enter into Freud's thought on the great questions of civilization and the instincts and the role of science within human culture. On both of these issues, as on the question of morality, Freud displays a pervasive ambivalence that is the direct product of his ambivalence about, and anxiety concerning, women. (p. 62)

Sagan then discusses the importance of the preoedipal period of nurturing on a child's psychological development, a time he feels that Freud "repressed" in favor of the development of a "harsh, punishing, castrating superego" as the result of the oedipal conflict resolution (pp. 62, 63). Sagan continues with "a serious attempt to reconstruct a psychoanalytic theory of morality based on conscience as the primary moral mechanism in the psyche. Conscience, which grows directly out of the relationship of the infant and child to its primary caretaker(s)—that is, in most cultures, until today, the mother" (pp. 64–65).

This focus leads to a discussion of the anger men feel toward separation from the nurturing and controlling mother, an anger turned against all women sexually and socially. The anger has its origin in the mother's suppression of the child's eroticism. Sagan says that a child's conscience will develop according to the adequacy of the nurturing by his or her parents. Children thus learn to give back love and caring and finally to be loving toward others as well. "Basic love is not the result but the foundation of conscience" (p. 63). "The capacity to identify with both nurturer and the victim is essential to both conscience and a healthy psyche. This conclusion never could have been reached by a psychoanalytic theory restricted to oedipal and postoedipal life" (p. 181).

Sagan then discusses the need for children to absorb both the good and the bad in their parents through identification and idealization and in resolving this ambivalence to come up with their own sense of morality and conscience. "There always remains a part of the psyche that knows that only loving attitudes and the control of aggression are truly moral" (p. 200). However, one must be able to come to moral decisions through a capacity for independent judgment. The child must learn that he or she can question parental values and, later, those of society without fear.

The final section of the book deals with the system of values in a society, as distinct from the moral system, and leads to a discussion of the questions faced in the United States, especially, today. Sagan says that "aggression is the fundamental human problem, morality and love the fundamental cure" (p. 243) and concludes that the attributes of a new, more moral society would emphasize the qualities that frighten men—feminine qualities such as nurturing, a sense of community, love for children, equality over tyranny. Only in this way, he feels, will we avoid annihilation through man's aggression.

I began reading this book with much interest and found the first chapters enjoyable and thought provoking. However, the ideas soon became repetitive, and my concentration wandered. The author has a pronounced tendency to lecture the reader, like a professor before an undergraduate class, constantly reemphasizing his points. This distracts from his presentation and unnecessarily lengthens the book. At one point Sagan states that the reader will work through the ensuing chapter and at times it was arduous, not in following the theories but in following the prose.

Any therapist interested in a psychodynamic approach to the problems of inequality between men and women will find this book of interest. Since I am not an analyst, I am not prepared to comment on the validity of Sagan's analysis of Freud's original theories. As a psychotherapist, I found his arguments persuasive but I was struck by the simplicity that is always inherent in a single explanation for human behavior. The book left many questions unanswered in my mind. Although I feel that it is very necessary to understand the cultural context in which Freud lived, we would have benefited more from a greater discussion of the German philosophers who influenced Freud in his thinking in addition to the analysis of the society that Sagan provides. In addition, I was somewhat curious about his emphasis on early Greek and Roman cultures and then a leap to the 1600–1800s, with very little about the periods in between.

Overall, I think this is a book well worth reading. It is a good addition to the current literature as we continue to struggle toward an acceptance of women's place as equal to that of men.

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Psychoanalytic Treatment: An Intersubjective Approach, *by Robert D. Stolorow, Bernard Brandchaft, and George E. Atwood. Hillsdale, N.J., Analytic Press, 1987, 187 pp., $22.50.*

There is little doubt that the current psychoanalytic scene is in a period of creative ferment. Freed from the theoretical reifications and anachronisms of classical metapsychology, psychoanalytic clinical theory is bursting forth with renewed and unexpected exuberance. A stream of contributions document newer developments in psychoanalytic theory and therapy (1–4).

Psychoanalytic Treatment: An Intersubjective Approach is the latest contribution in an impressive line of clinical reformulations, elaborations, and applications of Kohut's self psychological theory (5–7). As interpreters of Kohut, Stolorow, Brandchaft, and Atwood self-consciously see their task as furthering "Kohut's goal of reframing psychoanalysis as an empathic-introspective depth psychology of human subjectivity" (p. 27). Consistent with an emerging trend in psychoanalysis, they advocate an "experience-near" type of clinical conceptualization and cleanse Kohut's theory of the last vestiges of mechanistic, "experience-distant" abstractions and reifications. Additionally, the authors advocate and elaborate a fundamentally phenomenological, intersubjective approach to psychoanalytic therapy. The intersubjective approach rejects the view that pathology is due to mechanisms and processes located solely within the patient, emphasizing the role of reciprocal mutual influence in the genesis and cure of psychopathology. In this light, clinical concepts such as transference, resistance, psychic conflict, affective development, borderline states, and psychoanalytic cure are reworked.

Therapeutic change is conceptualized in this framework as the patient's response to the empathic climate that characterizes the psychoanalytic interaction. In a new and likely to be controversial reformulation, the authors stress the "selfobject" dimension of the transference. Although this approach to transference encompasses the traditional elements of displacement, projection, and repetition, the authors view transference as the necessary replication of early life conditions with caregivers that traumatically engendered developmental derailment and fixation. In contrast to Kohut's view, "selfobject transference" is not a type of transference but a dimension of all transferences. In this formulation, transference becomes a crucial, curative vehicle and point of departure for the resumption of arrested psychological growth.

Psychoanalytic Treatment: An Intersubjective Approach is an indicator that psychoanalysis is a vital, pluralistic discipline with an increasingly strong clinical focus. The book is a lucid reformulation of psychoanalytic theory from the perspective of an established and evolving self psychology. A rich humanism pervades the work, placing it in stark contrast to the alarming recrudescence of an objectifying focus on "pathology" and the devaluation of subjective experience as byproducts of biochemical processes.

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Psychotherapy: The Art of Wooing Nature, *by Sheldon Roth, M.D. Northvale, N.J., Jason Aronson, 1987, 288 pp., $27.50.*

This is an exceptionally fine work on dynamic psychotherapy by a gifted clinical writer who presents a cohesive and informed thesis with an uncommonly clear and accessible style. There is something valuable here for nearly everyone in our field, whether neophyte or senior clinician. This volume is a welcome addition to a long line of distinguished contributions to the psychotherapy literature by Colby, Tarachow, Dewald, Basch, Luborsky, and others.

Rather than beginning with theories of therapy or psychopathology, Dr. Roth starts by focusing on what the patient and the therapist each bring to the treatment situation. From the first chapter he explores territory where others rarely go. Compelling questions about the personality of the therapist are addressed here and throughout the book: Who would want to do this kind of work? What is actually required to become an able psychotherapist? Which countertransferences enhance or impede the progress of psychotherapy?

Dr. Roth underscores the durability that is required of the therapist in order to face facts and bear hostile affects while maintaining appreciative empathy for the patient's suffering. He details an array of therapist styles and capabilities, suggesting that there is a wide spectrum of patient-therapist matches for optimal therapy. He also reminds us that it is unlikely that we will be able to work effectively with all types of patients throughout our careers, that our own idealized transferences to teachers and supervisors, which he calls "training transferences," are often constraining, and that personal therapy is an essential ingredient in the making of a psychotherapist.

The book's principal contribution is in the rediscovery of and emphasis on transference as a core phenomenon in psychotherapy. Here Dr. Roth is very eloquent: "The keen clinician has respect for transference as the compendium of summarized history of the patient, and trusts the transference to emerge in such a form as to lead both patient and therapist to the clinically relevant events and conflicts of psychic life. Recognition and empathic tact in the handling of the resistance element of transference are cardinal." Throughout the book readers are shown how the thread of the transference can be followed and used productively with many kinds of patients to chart progressive or regressive developments during treatment.

Once this basic focus is established the book moves into useful discussions of the stages of treatment, the central position of loss and mourning in symptom formation, the special role of dreams in psychotherapy (this chapter is a tour de force), combining psychotherapy and pharmacotherapy, gender issues that may bias psychotherapists, and many practical aspects of doing psychotherapy (the office setup, the telephone, etc.).

Dr. Roth illustrates most of his clinical points with memorable vignettes involving patients with all levels of ego strength and many diverse diagnoses. T.S. Eliot's verse, Rabbi Nachman's tales, and many other contributions to literature and culture are creatively woven in and enhance the book's theses. Finally, a wonderful annotated bibliography of treasured papers and books by psychiatrists and psychoanalysts with varying orientations (classical psychoanalysis, self psychology, and object relations theory, for example) is provided, and the views of many of Dr. Roth's own teachers (Semrad, Tartakoff, Zetzel) are cited throughout the book.

As the author points out in the final chapter, patients generally describe their treatment as successful, not in terms of specific insight that is gained but by the new presence of a "central emotional feeling toward the experience" of psychotherapy. *Psychotherapy: The Art of Wooing Nature* offers readers an analogous grasp and feeling about the process of psychotherapy. This is a very special book. I hope that it will leave an indelible mark on the teaching and practice of psychotherapy in psychiatry.

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Raise Your Right Hand Against Fear, Extend the Other in Compassion, *by Sheldon Kopp. Minneapolis, CompCare, 1988, 154 pp., $8.95 (paper).*

This is Sheldon Kopp's fourteenth book. He has indicated in the past that, in part, he writes as therapy to keep himself occupied and distracted from his serious medical problems. I have been a long-term Kopp fan and have read all of his works. For me, it is an important publishing event when Sheldon Kopp produces a new book. I have regarded him as a cherished mentor over the years and very much enjoy reading what he has to say. I feel that I can always count on Kopp to give me meaningful food for thought.

The audience of this latest venture is not made clear to the reader. I suspect that, in view of the publisher, it is intended to be disseminated to drug abusers. Further support for this notion is derived from occasional references in the body of the work to addiction and factors in addiction. However, I prefer to think of this book as I do of many of Kopp's other works as intended for every person. Kopp seems to have a ready knack for describing the human condition using liberal personal examples.

As the title suggests, *Raise Your Right Hand Against Fear, Extend the Other in Compassion* is about fear and dealing with fear. The closest that I am able to come to a purpose is Kopp's statement, "In this book I hope to offer readers an understanding of apprehensions they might otherwise ignore, so that they can learn to cope in ways that will open them to discovering new options for themselves." Kopp includes a number of stories derived from popular literature, all designed to shed light on the human condition and how human beings express and cope with fear. In the course of the book, Kopp develops a number of themes on the human condition and presents for the reader's benefit a number of recommendations related to dealing with fear. Sample themes include seeking other people's approval and attempting to avoid disapproval; the commonality of human fears (the idea that we all fear much the same things); the idea that all of us contain a dark side (the "beast" in us), which we are better off owning than denying; the concern about becoming an independent, self-directed being and what others will think of this; and the idea that no one can escape from illness and injury or aging and death or worry about the welfare of loved ones.

As to recommendations, a sample of some especially thought-provoking gems follow. 1) We must learn to face our fears directly, develop courage, indulge curiosity, and improvise an adventuresome life style. 2) Develop additional options for yourself, cultivate the option of doing as you please. 3) Weigh whether delaying further action will make the situation any safer for you. 4) Accept and own the dark side of yourself so that you can control it rather than being at the mercy of it.

Having read so much of Kopp, I must confess that there is a familiarity about what he has to say in this book. However, it never ceases to amaze me how clearly and concisely Kopp can say something that hits the mark. He has a terrific ability to coin a phrase, so to speak. Some of the examples I shall list here relate to themes and recommendations already discussed. Herewith are some of my favorite Koppisms contained in this work: "Stubbornness is strength that has not been let loose." "We must be willing to tolerate the holy insecurity of uncertain outcomes that accompany taking chances." "It takes one kind of courage to wait patiently and another to get on with it." "You have managed to hide yourself so well that now you are afraid that no one will ever find you." "If our best efforts bring failure, we shall fear no evil because it is not our fault." "As life keeps coming at us, there are times when we either learn to laugh at ourselves or we end up feeling frightened to death." "Most of us are not all we pretend. Certainly none of us is just what we were taught we were supposed to be." "There is no shame in doing things the easy way." "Whatever we wish to believe about ourselves, somewhere inside the opposite is also true."

There is more of this sort of thing. The reader is invited to join this latest feast and discover additional favorite aphorisms. For readers unfamiliar with Sheldon Kopp, this short work might be a good place to discover him. For old Kopp fans, reading this short work is like getting reacquainted with an old and familiar friend. I continue eagerly to look forward to each additional work from Sheldon Kopp.

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BEHAVIORAL MEDICINE

Pain and Disability: Clinical, Behavioral, and Public Policy Perspectives, *edited by Marian Osterweis, Arthur Kleinman, and David Mechanic (Institute of Medicine Committee on Pain, Disability, and Chronic Illness Behavior). Washington, D.C., National Academy Press, 1987, 292 pp., $24.95 (paper).*

The saying "A camel is a horse made by a committee" is intended to show that the end product of a committee's work can be uneven due to compromise and varied input. This book is a product of a committee, but it is a horse, not a camel, and a good horse at that.

The origins of the book deserve special mention. During 1980 and 1981, the Social Security Administration (SSA) intensified its reviews of disability cases, resulting in a "purging" of its rolls that caused strong and antagonistic public, judicial, and Congressional reactions. In 1984, Congress amended the Social Security Act to include for the first time a statutory standard defining the way in which pain should be evaluated by the SSA in determining eligibility for disability benefits. It also legislated that the Secretary of the Department of Health and Human Services appoint a Commission on the Evaluation of Pain. The commission's life was short, and it recommended that the Institute of Medicine continue the study of these issues. To accomplish this, the institute appointed the Committee on Pain, Disability, and Chronic Illness Behavior. This committee was asked to explore the relationship between medical illness and pain, the connections between pain and function, and their relation to illness behavior as well as the ways in which disability benefit programs deal with the symptoms of chronic pain. It was also asked for suggestions in measuring pain and dysfunction and how the benefit structure and administrative processes of SSA might affect pain complaints. It was expected that the committee would make recommendations for improvement in the way SSA deals with pain and suggest areas of research for the better understanding of chronic pain. Set with these noble tasks, and after many months of deliberation, the committee wrote this book, which contains its findings and recommendations.

This volume tells the reader what is known about the connection between pain and disability in terms of clinical, behavioral, and public policy issues. The subject is a difficult one. There is no clear relationship between the amount of tissue damage on the one hand and the degree of discomfort, pain, and disability on the other. Many psychosocial issues influence the degree of experience of pain and discomfort as well as the degree of disability resulting from these symptoms. For example, strain may cause muscle contraction that may increase or exacerbate a pain problem. Different ethnic groups respond differently to the same amount of tissue damage. Underlying personality disorders, psychiatric diagnoses, and psychiatric symptoms place some individuals in more vulnerable positions in respect to pain. These include affective and somatoform disorders, substance abuse, and hypochondriasis. Since there is no method to measure pain and no linear connection among tissue damage, pain, and disability, the task of determining disability associated with pain is exceedingly difficult. In actual practice, disability is never determined solely by pain without a known underlying cause. The definition of disability in the Social Security Act is more restrictive than other disability compensation programs, both in the United States and in other countries. The SSA requires for disability the inability to work at "any substantial gainful activity" because of medically determined physical or mental impairment that is expected to either cause death or last 12 months or longer.

The book carefully describes the process individuals go through in order to have SSA determine their disability. It describes program benefits, incentives for rehabilitation, and return to work as well as how pain has been handled by the courts. The extent and cost of the problem is staggering. In 1985, $18,000,000,000 was paid to 2,600,000 persons in the United States as a result of SSA determinations of disability.

The committee makes six sets of recommendations. 1) The SSA should develop a better system for routine data collection and information retrieval for disability programs. 2) Neither "chronic pain syndrome" nor "illness behavior" should be added to the regulatory list of impairments. 3) Significant pain should trigger an assessment of the capacity of the individual to work. 4) The SSA should design major evaluation projects to compare different methods of early evaluation of pain in claimants and to assess the efficacy of early rehabilitation interventions with chronic pain patients. 5) The Secretary of the Department of Health and Human Services should engage in broad research efforts on pain and disability in cooperation with other federal agencies. 6) The training of health care professionals should foster a comprehensive and multidisciplinary approach to patients with pain.

This is an interesting, well-written book that comprehensively and successfully undertakes a difficult mission. It has great value for professionals involved in working with individuals who are either disabled or may be involved in the process of disability determinations.

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Biological and Psychological Factors in Cardiovascular Disease, *edited by T.H. Schmidt, T.M. Dembroski, and G. Blümchen. New York, Springer-Verlag, 1986, 623 pp., $52.00.*

This book is an outgrowth of a conference held in Germany on stress and cardiac illness. The presentations were primarily by cardiologists, physiologists, and psychologists. The editors are leaders in the field, and most of the contributors are well-known investigators. It is the interdisciplinary nature of this volume that is both its strength and its weakness. The principal strength is the encyclopedic coverage of this field; the weakness is that the diversity of approaches vitiates any meaningful synthesis of the conceptual and empirical material.

The book is well organized into five sections. The first deals with psychosocial factors and coronary heart disease and contains a comprehensive review of the type A behavior pattern by Rosenman and a useful paper by Engel questioning whether type A is a behavior or a trait. In the latter paper, the variety of methodological traps that confront researchers in this area is succinctly presented. The multifactorial nature of type A behavior, the uncertain relationship between questionnaire results and structured interview data, and the lack of relevance of laboratory studies to actual life experiences confound most research.

The second section is entitled Cardiovascular Psychophysiology. Of note here is Dimsdale's paper, "New Dimensions in Studying Sympathetic Nervous System Responses to Stressors." This work elucidates the successful modification of some type A behavior by clinicians using β-blockers and clonidine. The paper by Payne and Rick, "Psychobiological Markers of Stress in Surgeons and Anaesthetists," is a fascinating study linking specific stressors in these specialists to high levels of cortisol and vanillylmandelic acid.

The third section of the book, which deals with psychophysiological mechanisms in hypertension, atherosclerosis, and sudden cardiac death, will be of primary interest to investigators with this focus. The same can be said of the chapters in the fourth section, which is concerned with animal models. The potential relevance to human disease of attributes such as dominance, submission, and aggression is explored in studies with a variety of species.

Psychiatric clinicians will find themselves most enthusiastic about the fifth section of the book, Prevention and Control. This section has relevance to the psychiatrist interested not only in prevention but in treatment of patients who have experienced myocardial infarction or cardiac surgery. The roles of relaxation training, endurance training, and medication are explored in several chapters. Psychiatrists with experience in cardiac rehabilitation may wish to see this section expanded into an entire volume. Such specific areas as comprehensive treatment of anxiety and depression and monitoring of quality of life in patients with various types of cardiac disorders could be included. This will have to await future clinical research and proceedings from symposia.

A good deal of this book travels well-worn roads. New research paradigms are needed in this work but are unlikely to occur without general and biological psychiatrists involving themselves in this field and supplying much of its substance in the future. Although the book does not dispel the uncertainties and controversies within this field, it does represent the most powerful current scientific approaches to an understanding of the psychosocial aspects of cardiovascular diseases. This volume is an excellent reference for researchers and is of modest utility to clinicians with an interest in this important area.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Clonazepam for the Treatment of Stupor in Catatonic Schizophrenia

SIR: Several recent reports (1–3) have dealt with the use of lorazepam therapy for catatonic schizophrenia. According to our experience in the acute treatment of some of the negative symptoms of catatonic schizophrenia, clonazepam may produce results very similar to those of lorazepam. In a sample of four catatonic schizophrenic male inpatients, diagnosed according to *DSM-III* criteria, the administration of intravenous clonazepam produced very positive acute results.

> Mr. A, 23 years old, had been treated for the past 3 years with neuroleptics for his negativism and mutism. After he experienced a 4-hour-long stupor with fixed posture or movement (catalepsy), he was given 1 mg of clonazepam intravenously, and the stupor disappeared within 5 minutes. Mr. A has had no catatonic state with psychomotor retardation since he began a regimen of oral clonazepam, 3 mg/day.
>
> Mr. B, 25 years of age, had been under neuroleptic treatment for 3 years for eccentric behavior and emotional blunting and, later, for several stuporous episodes that lasted for hours or up to a day. The administration of clonazepam, 1 mg i.v., resulted in rapid improvement of his severe psychomotor retardation with catalepsy and mutism. His negativism and catalepsy disappeared and communication resumed.
>
> Mr. C, 28 years old, who had been drug free for 6 years, was hospitalized for catatonic excitement (perseveration and jactation) alternating with psychomotor retardation (mutism, negativism, and catalepsy). His 4-hour episode of mutism and bizarre forward-backward swinging movement stopped 5 minutes after the intravenous administration of 1 mg of clonazepam, and from then on he could converse as well. A regimen of oral clonazepam, 2.5 mg/day, prevented the serious excited and inhibited catatonic symptoms from reappearing.
>
> Mr. D, 18 years of age, had been in a mute and negativistic state with daily episodes of catalepsy for over a year. When clonazepam, 1 mg i.v., was administered, the mutism disappeared within 5 minutes, and the effect lasted for the next 4–5 hours. The patient could converse and speak about the delusions from which he suffered.

The experience we gained from these cases in which patients in acute stuporous and inhibited states—two of whom had had previous basic neuroleptic treatment that led to no improvement whatever—received clonazepam intravenously leads us to the following conclusions. 1) Clonazepam can rapidly dissolve catatonic, inhibited states and thus replace ECT. 2) No difference in reaction to intravenous clonazepam was observed between patients who had previously received neuroleptic medication and those who had not. 3) Lasting clonazepam medication may prevent catatonic, inhibited (negative) symptoms from surfacing. 4) The fact that some benzodiazepines are effective in the treatment of stuporous catatonic states suggests that the pathogenesis of schizophrenia may be partly attributable to a complex disregulatory disorder in the brain neurotransmitter system, thus, we suppose, involving the γ-aminobutyric acid (GABA) system as well.

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Depression in Patients Receiving Lorazepam for Panic

SIR: We previously reported the emergence of depressive symptoms in patients receiving alprazolam for panic disorder (1). There have also been reports of the emergence of depressive symptoms in patients being treated with bromazepam or lorazepam for generalized anxiety disorder (2) and with clonazepam for panic disorder (3). We now report the emergence of depression in patients receiving lorazepam for panic disorder.

We (4) and others (5) have recently reported that lorazepam appears effective for treating panic disorder. Although lorazepam adequately controlled panic, we observed the emergence of depression in several patients taking low to moderate doses of the drug. Of the 30 patients who completed at least 6 weeks of lorazepam treatment (average dose=3.75 mg/day; range=1.5–6 mg/day), eight (26.7%) developed symptoms that met the *DSM-III* criteria for a major depressive episode. Three other patients also had symptoms of depression that did not meet *DSM-III* criteria (i.e., they had fewer than four depressive symptoms or the symptoms lasted less than 2 weeks). Of the eight patients who developed a major depressive episode, three reported a single previous major depressive episode, one had had two previous major depressive episodes, and one had been diagnosed as dysthymic. Three of the patients denied any previous history of depression. Family history of depression was denied by four patients; the remaining four reported a family history of unipolar depression.

Four patients developed depression within the first 6 weeks of treatment, two developed symptoms after 3–6 months of treatment, and two after 6–9 months of treatment. The three patients with minor depression developed symptoms within the first 6 weeks of treatment. No patients developed suicidal ideation and none attempted suicide. In all cases, depressive symptoms were initially treated by decreasing the dose of lorazepam, and the depressive symptoms resolved within 1–2 weeks without recurrence of panic in four of the eight patients. However, for four patients with major depression, either depressive symptoms did not resolve or panic attacks recurred after lorazepam doses were decreased. These four patients improved when imipramine or desipramine was added to their treatment regimens.

The emergence of a major depressive episode in 26.7% of our lorazepam-treated panic disorder patients is quite similar to our finding of a 33% rate of major depressive episodes in panic disorder patients receiving alprazolam (1). Depressive symptoms usually emerged during the second or third week of treatment; no diagnosis of major depressive episodes was made in these patients. Whether lorazepam promoted depressive symptoms or simply failed to prevent their emergence is unclear.

Similar to our findings in alprazolam-treated patients (1), lorazepam blocked panic attacks effectively in most of our patients but did not prevent the emergence of a major depressive episode in about one-fourth of the patients. Lowering the dose of lorazepam relieved depressive symptoms in most of our patients, although panic attacks recurred in some patients whose doses were lowered. Clinicians who use lorazepam to treat panic disorder should be aware of this possible complication.

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Bulimia That Predates Restricting Anorexia Nervosa

Sir: Bulimia nervosa, anorexia nervosa with bulimia, and restricting anorexia nervosa overlap in some patients. Bulimic patients often have histories suggestive of anorexia nervosa (1, 2), severe dietary restriction sometimes predisposes to binge eating (3), and bulimic anorexic patients with the bulimia predating the anorexia nervosa have been described (4). This letter describes progression from normal-weight bulimia nervosa to restricting anorexia nervosa.

Ms. A, an 18-year-old college student, was 5 ft 6 inches tall and weighed 90 lb, approximately 70% of her ideal weight. At age 14 she had begun binge eating monthly with friends, consuming large quantities of high-calorie foods. The binges gradually increased to five times daily. At 17 years of age she reached her maximum weight of 130 lb, and vomiting, which had previously been rare, now frequently followed binges. Dysphoria, guilt, and depression occurred after binges, and the binge-vomit cycles became "evidence" of her ineffectiveness and poor control. Ms. A reduced her intake to low-calorie "safe" foods, adhering religiously to three bland meals (totaling 500 calories) daily. Each day she also exercised for 90 minutes and used a laxative. Although unsatisfied with the 25-lb weight loss that ensued over the next 6 months, she spoke with pride about discontinuing her binge-vomit cycles. She was obsessed with food, weight, and dieting, denied being too thin, and feared that eating would potentially induce binges and weight increase. Her social activities declined, but not her school performance.

Ms. A's upper-middle-class family was without a history of depression, substance abuse, or obesity. Her pertinent medical history included mild cold intolerance and secondary amenorrhea. Results of appropriate laboratory studies were normal. Mental status examination revealed euthymic mood without disorder of thought form or content. Her thinking patterns about food, weight, and dieting were consistent with her eating disorder. Compulsive personality traits were noted.

Ms. A's individual therapy included cognitive behavioral techniques focused on weight, dieting, self-esteem, body image, and control issues. She also attended supportive group therapy. In 6 months, with much support and a slowly increased caloric intake, she gained 22 lb, her menses returned, and there was no binge or purge behavior. Emotionally she did well, accepting and maintaining her 112-lb weight while maintaining euthymic mood, high academic achievement, and an active social life. At 2-year follow-up she was still doing well, eating normally without binges or purges, and maintaining her weight at 120 lb.

Garner (5) noted that although they do not usually articulate it, "some bulimic patients essentially request to be converted to restricting anorexics (i.e., sub-menstrual weight and rigidly controlled eating)" when seen for therapy. However, in our clinical experience, restrictive dieting is incompatible with controlling binges because of the associated intense hunger. In this unusual case, the patient's pronounced dislike of binge eating, coupled with compulsive traits, facilitated creation of her restrictive, more ego-syntonic eating pattern. In addition, the three carefully spaced meals and daily exercise may have moderated her appetite, while the weight loss reinforced the pattern. This progression from bulimia to restrictive anorexia nervosa may be recognized more frequently as additional longitudinal therapy experience with these patients is gained.

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The Cost of the Split Between Psychodynamic and Psychobiological Perspectives: A Resident's Point of View

SIR: I was an intern in psychiatry at Duke University Medical Center and am now completing my residency at the Menninger Foundation. To the resident, the division of opinion among many attending physicians about whether a case is predominantly a psychodynamic or a psychobiological phenomenon seems puzzling. Why is there such a need to polarize, when the patients we treat are so obviously an integration of both factors?

This is more than a teaching issue. A patient with sciatica has a diagnosis of somatization disorder through 6 years of psychiatric treatment because no one performed a detailed neurological examination after an episode of physical trauma. At the other extreme, a patient with a 20-year history of anxiety who is taking high doses of benzodiazepines is told that the anxiety is due to a familial tremor, is prescribed propranolol, and is discharged after 3 weeks without referral for psychotherapy.

Residents in training would benefit most from teachers who demand of themselves competence and thoroughness in both the biological and psychodynamic evaluation of patients. Without such role models, residents feel pulled to align themselves with one perspective or the other, and the split is perpetuated.

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Overuse of the Term "Acting Out"

SIR: We agree with Glen O. Gabbard, M.D., in the article "Splitting in Hospital Treatment" (1) that the term "splitting" has been misused and overused to the point that its specific meaning is in danger of being lost. In our experience, the term "acting out" is being similarly overused. While it specifically refers to a defense mechanism involving "the direct expression of an unconscious wish or impulse in action to avoid being conscious of the accompanying affect" (2), we note informally that it seems now to be used in reference to virtually any misbehavior exhibited by children or adolescents. We urge clinicians to reserve the use of both "splitting" and "acting out" for occasions in which postulated dynamic mechanisms are being referred to. Descriptions of maladaptive behaviors such as temper outbursts may best be made by using explicit behavioral terms.

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Treatment of the Severely Mentally Ill Poor

> Do justice to the poor and fatherless;
> Deal righteously with the afflicted and destitute.
> Rescue the poor and needy. (1)

SIR: This letter is meant to beg further inquiry into the psychiatric treatment of the severely mentally ill poor in city/county and state hospitals, where most of these individuals are admitted (2, and personal communication from K.H. Rey, 1989) and where, in the case of state hospitals, some of them reside for up to decades. Because of my institutional affiliation (Harlem Hospital, New York City), the research data on which I base these comments focus largely on the black population.

Illness can destroy life and prevent the full flowering of the individual. It is my observation that remission of mental illness (especially, acute exacerbations of chronic states) among the poor is not prized highly or sought aggressively enough. Factors in this situation include public hospitals' mandate to speedily filter patients through the system (sometimes irrespective of the patients' remission status at discharge) and adherence to a measure of physician "productivity"; use of fixed and irrevocable psychopharmacologic regimens (perhaps above therapeutic windows) that wait for the patient to get better rather than individually tailored regimens that aggressively pursue remission on a daily basis; use of the term "stabilized" as a measure of treatment success; implicit or explicit pronouncements on patients' "deviance" when they are compared to mainstream Americans and when they do not exhibit desirable ward behavior; therapeutic nihilism; and manifest disrespect and lack of emotional support for the poverty patient (often on the part of other minority individuals). Not infrequently, the patient and his or her disease receive the blame for therapeutic failures. Lives are held in the balance.

The full impact of the failure to produce remission of mental illness among the severely mentally ill poor is unknown and untold at this time. Causes and consequences seem to include 1) in comparison with white people, black people's significantly higher risk of poverty, rate of male unemployment, percentage of households headed by single-parent women who have difficulty in finding appropriate outside work, percentage of out-of-wedlock births, rate of low-birth-weight infants, and rate of school dropouts; 2) the acknowledged effects of illness and disability on job procurement and maintenance (3); and 3) the inverse relationship between socioeconomic status and the prevalence of serious mental illness (particularly schizophrenia) (4).

There seems to be no known, direct causative link between poverty and mental illness; perhaps one exists between mental illness and neediness. Multigenerational poverty seems intransigent at this time (3, 5); the production of remission, I feel, is not. Are we giving our poor, severely mentally ill patient every opportunity to love and to work? As Thoreau wrote, "How much virtue there is in simply seeing."

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Dosage of Oral and Depot Fluphenazine

SIR: By using an arbitrary conversion factor for depot and oral fluphenazine, Lawrence B. Inderbitzin, M.D., and colleagues (1) appear to have created "a clinical problem" where none exists. The plasma concentration of fluphenazine in patients taking an oral dose of 10 mg/day is much higher than that in patients taking a 12.5-mg dose of fluphenazine decanoate every 3 weeks, and the pharmacokinetics of the two dosage forms are completely different (2, 3). Furthermore, steady-state plasma levels in patients who are initially stabilized on a regimen of oral fluphenazine and then switched to the decanoate form fail to show a consistent relationship, thereby precluding prediction of the dosage requirement when changing to the depot version from the oral (4). For these reasons, no conversion factors, whether based on clinical comparisons of oral neuroleptics or on in vitro receptor potency (5), are satisfactory.

A more meaningful comparison between depot and oral medication would be in terms of the total amount of drug absorbed in a given time by a patient taking average antipsychotic doses of each. For example, a patient switched from 10 mg/day of oral fluphenazine to 12.5 mg every 3 weeks of the depot drug would formerly have been receiving 210 mg over 3 weeks, which, allowing for a first-pass metabolism effect possibly as high as 80% (6), still indicates a residual drug exposure of 42 mg. From these considerations it is clear that patients would normally be exposed to much less drug when switched from the oral to the depot version.

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Chronic Marijuana Use by Adults: A Rebuttal

SIR: In the November 1988 issue of the *Journal*, in the Book Forum section, Rick J. Strassman, M.D. (1) gave a very biased and misleading book review of *Living High: Daily Marijuana Use Among Adults* by Herbert Hendin et al. The book describes a survey of 150 adults who smoke marijuana frequently and includes in-depth vignettes of 15 adult daily marijuana smokers. After I read the review, I had to reflect on whether Dr. Strassman had discussed the same book that I had previously read from cover to cover. Instead of pointing out the subjects' success in their careers and the rather benign adverse effects of their use of marijuana, which were selectively noted by the reviewer, the authors themselves reached very different conclusions.

Dr. Strassman ended his review by noting that "the book . . . is a valuable contribution to our understanding of the relatively benign effects of one drug on the psychosocial functioning of middle-class adults." Some examples from the book will illustrate that Dr. Strassman's summation was inaccurate. Forty percent of those interviewed used marijuana at the start of working days, 30% smoked the drug while at work (including some of the six individuals who were bus, truck, or taxi drivers), and 73% regularly smoked the drug while driving cars (1, p. 41). Forty-seven percent of those interviewed wanted to cut down or stop smoking marijuana; 75% stated that nearly all of their friends were regular users of marijuana (p. 41), 51% used cocaine occasionally, and 9% were regular users of cocaine. Fifty-seven percent of those interviewed had never married, and only 21% of the total group had children.

Through the intensive study of the 15 selected subjects, the authors saw how difficult it was for these subjects to experience pleasure, how seldom they really felt good, how often they felt low rather than high, and how difficult it was for them to relax. On page 162 of the book, the authors concluded that problems in close relationships were present in virtually all of the adult daily users of marijuana. Particularly striking was the fact that in almost every case, the MMPI results pointed to the daily marijuana-smoking individuals' need to deny their significant problems and to present themselves in the most favorable light. Those who functioned effectively and responsibly at work seemed to see the responsible side of their personality as a constraint against which they struggled (p. 164).

An in-depth review of the case of the corporate attorney (the most outwardly successful of the subjects studied) revealed the following information: this successful corporate attorney had smoked two or three "joints" a day for almost 20 years, had been divorced twice, saw his children on a fairly limited basis, and described himself as treating his subordinates "like dogs." Marijuana made it unnecessary for him to look at himself or to see any flaws. He had virtually excluded all reading from his life for many years and showed a significant deterioration in his intellectual functioning on the WAIS-R.

Dr. Strassman has done a disservice to psychiatrists who may not have the time to read *Living High*. He stated that the adults in the study did not use marijuana in a self-destructive way and were not damaged by their regular use of the drug. Inaccurate interpretation of the harmful effects of marijuana by professionals like this reviewer has done much to promote the widespread use of the drug by children who have not even reached high school age.

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Integrating the Psychotherapies

SIR: The authors of the recent special article on integrating the psychotherapies (1) are to be commended, and so is the *Journal*, because the topic is vitally relevant to the evolution of our profession. As awkward and semantically "loaded" as the term "eclectic" is, most professionals think of themselves in this fashion and most residents seek training programs that offer an eclectic orientation. A theoretical foundation needs to be more widely agreed upon if the demands generated by these trends are to be met. To succeed in realigning ourselves with the mainstream of medicine, it is essential that we begin to use a multimodal approach to address the diversity of psychiatric disorders and the individuality of patients.

Dr. Beitman and associates called for a unifying psychosocial language and, happily, there exists one that can function as an integrative general system: role theory. This approach, a uniquely American contribution to the social sciences, offers the potential for fulfilling most of the criteria mentioned in the article. Leaders in psychiatry, such as Ackerman (2) and Spiegel (3), and in social work, such as Perlman (4), have found this language useful because it alone can adequately describe phenomena at several levels of organization: intrapsychic, interpersonal, family, group, and cultural. I have systematized role theory to make it more clinically relevant and termed this modification "role dynamics" (5). I believe it can serve as the unifying bridge that Dr. Beitman and his colleagues seek.

Role dynamics has many advantages. Its language is relatively familiar and understandable, even to laypersons. It suggests the metaphor of life as drama, which in turn evokes a variety of useful associations. The concept of role implies a separation of the actor and the act, which is another way of thinking about the idea of the "observing ego." Most of the best insights of scores of current therapies can be integrated and translated into a common and simpler language. Role dynamics, which further functions as a rational foundation for a multimodal therapy, is itself associated with a host of methods (such as role playing) that have been adapted to many different kinds of treatment.

I have presented role dynamics at grand rounds in my department and would be happy to furnish additional information to anyone wishing to know more about this practical and rich complex of ideas. I hope the excellent article by Dr. Beitman and associates will stimulate other efforts in this direction.

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Medical Students' Attitudes Toward Cocaine Use

SIR: The article entitled "Cocaine Use by Senior Medical Students" (1) is important in calling attention to attitudes toward and use of this drug. We did a similar survey in 1969, which we reported in 1971 (2) and 1972 (3). Our sample consisted of 6,110 undergraduates from 10 colleges and 600 medical students from three medical schools of a state University. Of particular interest were our findings that 8% of the undergraduates and 7% of the medical students favored legalization of cocaine and that 17% of the undergraduates and 12% of the medical students would not disapprove of its use if it were legal. Five percent of the medical students at that time would have allowed younger siblings or their own children to experiment with the drug. Our primary focus in those studies was use of and attitudes toward cannabis, but we were concerned also with the effect of these attitudes on the spread of other illicit drugs. We quote from our concluding paragraph in the 1972 publication: "But are openness, acceptance and use of other drugs about to explode the way they did for cannabis in the middle 60's? Serious attempts at education, treatment and control of drug use must take into account students' views" (3).

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Compulsive Water Drinking and Water Intoxication

SIR: I read with interest the article "Self-Induced Water Intoxication and Alcohol Abuse" by Thomas L. Ripley, M.D., and colleagues (1). There is an error in the rates given for the occurrence of self-induced water intoxication. The authors correctly quoted Jose and Perez-Cruet's rate of 3% (actually 3.3%, with N=239) for water intoxication (2) but incorrectly cited a prevalence of 18% in Blum et al.'s study (3). In fact, Blum et al. showed a prevalence of 17.5% for compulsive water drinking in hospitalized males, on the basis of three random samples of urine specific gravities that were less than or equal to 1.008 (N=241). Ten of the 41 patients identified as compulsive water drinkers were studied in more detail, and at least four would seem to me to have had definite water intoxication at some time. One can thus estimate an approximate rate (for the occurrence of at least one episode of water intoxication in the sample group while hospitalized) of 7% (17.5% × 40%). Blum et al. did not do this estimation and did not give any figure for water intoxication in their study.

Clearly, water intoxication and compulsive water drinking are linked, but clinically they are separate phenomena. Cigarette smoking may be important in determining why some compulsive water drinkers go on to have periods of intoxication. The number of years of compulsive water drinking may also be significant. There are no established criteria for the diagnosis of either water intoxication or compulsive water drinking: the conditions are not mentioned in *DSM-III-R*, although several "intoxications" are given separate codes. The only possible classification of water intoxication would be 305.90, "other or unspecified psychoactive substance intoxication," but water is not normally considered a psychoactive substance. A condition that may occur in 3.3%–7% of long-term hospitalized psychiatric patients should have accepted diagnostic criteria.

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Dr. Koczapski and Associates Reply

SIR: We agree with Dr. Cooney that compulsive water drinking and water intoxication are separate but related phenomena. We share his concern that there are no clearly established diagnostic criteria for either. The whole area of polydipsia in chronic psychosis suffers from the lack of a precise and standardized terminology, as has been pointed out (1). It is for this reason that we used several objective and measurable criteria to categorize the water intoxication patients in our study. We welcome the opportunity to discuss these criteria in more detail.

For the past 5 years, we have operated a 30-bed inpatient water intoxication unit within an 1,100-bed psychiatric hospital. We also provide consultation on water dysregulation problems throughout the hospital. From our clinical experience, patients with polydipsia tend to cluster into four distinct groups.

First, there is a group with histories of one or more episodes of severe cerebral impairment (seizures, delirium, coma) who have serum sodium levels of 120 meq/liter or less. These patients have severe polydipsia (>10 liters/day). Both morning and afternoon urine specific gravities are 1.003 or less. Serum sodium levels vary diurnally, with afternoon values in the range of 120–130 meq/liter and morning values in the range of 130–140 meq/liter. Diurnal weight gains of 3–8 kg are present. This group is well represented in the literature, and probably corresponds to the 3.3% of chronic inpatients described by Jose and Perez-Cruet.

A second group shows milder disturbances of water homeostasis and cerebral functioning. This group may comprise up to 8% of chronic inpatients (2). These patients show diurnal weight gains of 3 kg or more but have no previous documented histories of hyponatremia, polydipsia, or water intoxication. On investigation, they show moderate polydipsia (5–10 liters/day). Urine specific gravities are below 1.005 in the afternoon but normal in the morning. Serum sodium levels vary diurnally, with afternoon hyponatremia (125–135 meq/liter). However, morning serum sodium values are consistently within the normal range. This group is not well described in the literature. It usually goes clinically unrecognized, as the hyponatremia and dilute urine are present only in the afternoon. We have suggested the term "water intolerance" to describe the apparently asymptomatic diurnal lowering of serum sodium levels in these patients (2).

A third group has mild polydipsia (3–5 liters/day) with no diurnal variation in weight or serum sodium. Water intoxication episodes occur rarely. During these episodes the serum sodium level is lowered, weight is increased, and urine is dilute. Clinically, the intoxication episodes may be severe, with symptoms such as violent attacks on others and impulsive self-harm. The episodes are transient and diurnal, and the values have returned to normal by the following morning. The only way to identify these patients is by ascertaining the serum sodium level or body weight during an episode of acutely disturbed or confused behavior.

The fourth group shows mild polydipsia but no other symptoms. The prevalence of polydipsia among long-term hospitalized psychiatric patients has been estimated to be as high as 60% (3).

These clinical groups could possibly form the basis for a rational classification of water intake problems.

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Splitting and Dissociation, Borderline Personality and Multiple Personality

SIR: "Splitting in Hospital Treatment" by Glen O. Gabbard, M.D. (1) was an excellent review of the theory and management of splitting, but it would have been more complete if it had included a discussion of the relationship between splitting and dissociation, borderline personality and multiple personality. When Freud once used the words "splitting" and "dissociation" in the same breath—"splitting of the mind and dissociation of the personality" (2)—he was expressing the intuitive similarity of these two concepts. The ability to split an inpatient staff is notorious not only in borderline patients but in patients with multiple personality disorder (3). The two disorders may appear so similar that *DSM-III-R* cautions, "Often the person with Multiple Personality Disorder is incorrectly diagnosed as having only Borderline Personality Disorder because the alternation of the personalities is mistakenly thought to be the instability of mood, self-image, and interpersonal behavior that characterizes Borderline Personality Disorder" (p. 272). How does Dr. Gabbard know whether Ms. A or Mr. D in his case reports had multiple personality disorder (4)?

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Dr. Gabbard Replies

SIR: I am grateful to Dr. Nakdimen for calling my attention to the close connections between splitting and dissociation, on the one hand, and borderline personality disorder and multiple personality disorder, on the other. I certainly agree with his observation that splitting is a common development in the hospital treatment of patients with multiple personality disorder. In fact, recent research (1) suggests that rather than being unique to borderline personality disorders, splitting is often associated with the inpatient treatment of personality disorders in general.

The traditional differentiation between splitting and dissociation has been that the former refers to structures (e.g., the ego or the self), while the latter refers to process (e.g., consciousness) (2). However, in actual practice the two terms are often used interchangeably. Indeed, from the standpoint of object relations theory, multiple personality disorder may be viewed as the most extreme form of splitting, in which the self-representations are so disconnected from one another that there is little or no awareness of the others' existence. Patients with multiple personality disorder share with borderline patients a marked disruption of self-continuity.

Although the differential diagnosis of the two disorders is often problematic, as Dr. Nakdimen suggests, several guidelines are helpful. 1) The split self-representations seen in the borderline patient usually do not appear as distinct personalities but rather as different aspects of one core personality. 2) The borderline patient has good recall of each self-representation and regards the contradiction with indifference or bland denial. 3) The predominance of a particular self-representation in the borderline patient depends more on the immediate object relational context than do the various personalities of the patient with multiple personality disorder. With the help of these guidelines and extensive information from hospital staff members, I was able to conclude that neither Ms. A nor Mr. D had multiple personality disorder.

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Do Not Go Gently Into That Good Night: More About the Junior Faculty Academic Dilemma

SIR: The recent description by Ellen Leibenluft, M.D., and associates of the academic dilemma of the inpatient unit director (1) invited comment from other academic medical directors. We were the successive medical directors of a geropsychiatry unit. One of us (B.Z.) had recently completed a geropsychiatry fellowship when he became the medical director (with Leibenluft and associates' dilemmas included) of the new geropsychiatry unit. To ensure that we could pursue our desired academic careers, the unit 3 years later became a clinical research unit, with a newly recruited medical director (J.T.), a senior faculty supervisor, a data manager, a research nurse, and a neuropsychology technician. In addition to having been a chief resident and director of an ambulatory center, the new director (J.T.) had served as a trainee on a research unit. The former director (B.Z.) stayed on as a team leader, but also to continue many duties of his previous role. Over the next year, 13 pilot projects were begun, systematizing already individualized patient care.

With the foregoing facts in mind, we wish to highlight Dr. Leibenluft and colleagues' strong exposition of the need to create a research environment. Research units allow junior faculty members to experience the necessary mix of teaching, clinical service, and research in trying to "make it" in competitive academic environments. In a research unit faculty members who can interact with senior outside faculty researchers do not burn out or feel that they are second-class citizens who must earn their way out of clinical care to the paradise of funded research projects. Unfortunately, creating such units (including ancillary staff and computer hardware), carrying out pilot research projects, reporting on them briefly but formally, and then obtaining outside funding can take considerable time (more than a year). Our own 26-bed research unit, which has been in service for 1 year, operates at 96% of capacity, with an average length of stay of 26 days, and our research personnel and computer hardware, both still to be independently funded, cost $86,000 and $25,000, respectively. Administrators and chairmen too often lack the patience to continue such departmental funding, which is often initially given with ambivalence. Moreover, we continue to strive for excellent care even as we demonstrate that this systematic clinical care, in addition to other unmeasurable payoffs, is research- and cost-effective.

Dr. Leibenluft and associates' remark that inpatient units are often "the best money maker[s]" ignores a financial aspect that exacerbates the director's dilemma at many levels, namely, the role of the director in "maintaining the census." Indeed, in addition to the director's many responsibilities, including patient care, it soon becomes clear that the director may have to do some postdischarge aftercare as well as community work to bring in patients (unless, of course, this role can be delegated to someone not embarrassed to render clinical care).

In conclusion, our own cooperative experience over the past year has surmounted some of the problems raised by Dr. Leibenluft and her colleagues. Unfortunately, their remarks about their experiences—eloquently and comprehensively stated—still arouse much affect among many junior faculty members in competitive academic settings.

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Legal Concept of Torts and Emotional Distress

SIR: Precision is valued in law no less than in science. "Legal Principles in the Psychiatric Assessment of Personal Injury Litigants" by Brian F. Hoffman, M.D., and Harvey Spiegel, LL.B. (1) invites clarification of several legal principles underlying modern tort law. A tort is not defined, as the authors stated, simply as a civil wrong but as a civil wrong *other than a breach of contract*, the second broad category of civil wrongs (2, p. 2). Torts are divided into those caused intentionally—among them the ancient torts of assault, battery, and false imprisonment—and those occasioned by negligence or without fault, concepts developed only more recently.

Award of damages for the emotional distress attending many intentional torts has long been allowed. Indeed, assault and false imprisonment presume no physical injury at all. An assault, in tort law, places another in imminent fear of harmful or offensive contact. (Actual contact is the separate tort of battery.) False imprisonment, also termed "false arrest," is the unlawful confinement of another. In both instances the primary item of damage is mental anguish (2, pp. 46–48).

Suits for emotional distress negligently inflicted have long been suspect under our law for several reasons: 1) difficulty of proof, 2) subtle and speculative nature, 3) evanescence, 4) individual variability, and 5) risk of opening the door to fictions, trivia, and arguments over bad manners (2, pp. 360–361). As noted by Magruder (3), "Against a large part of the frictions and irritations and clashing of temperaments incident to participation in a community life, a certain toughness of the mental hide is a better protection than the law could ever be." Thus, recovery of damages for negligent infliction of emotional distress in the absence of physical injury is traditionally reserved for those instances in which emotional distress is presumed to have occurred: the false report of the death of a close relative, the mishandling of corpses, or being within the zone of danger when another is physically injured (2, pp. 362–365). Exceptions exist, but in general, expansion of this type of liability has been very cautious.

No discussion of damages for emotional distress would be complete without mention of the tort of intentional infliction of emotional distress, fashioned by our courts in the 1930s to make possible recovery of damages for "extreme and outrageous conduct" calculated to cause mental anguish—often, although not always, as leverage to collect debts, avoid payments, or recover property. Occasionally, the motivation has been sheer cruelty or sadistic pleasure at the suffering of another. The classic case of this kind, a sort of legal curiosity, is the notorious "pot of gold," a proceeding that invites retelling before an audience of psychiatrists. In this case (4), pranksters buried a "pot of gold"—actually filled with the Freudian equivalent—for an elderly, eccentric, mentally deficient woman to discover. The pot unearthed, the victim was escorted with great ceremony to City Hall, where the pot was opened, to the amusement of the waiting throng. As Prosser and Keeton noted (2, p. 62, note 77), "The pot of gold came to her heirs, in the form of $500 damages."

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Dr. Hoffman and Mr. Spiegel Reply

SIR: We would like to thank Dr. Tobak for expanding on several areas of our article. There is always the danger, in trying to interpret the law or to make it understandable to a lay audience, that certain points will be left out or not given sufficient emphasis for the needs of every reader.

The distinction between assault and battery is important, and either can result in a tort action. It is also true that Magruder noted that suits based on emotional distress negligently inflicted have long been regarded with suspicion by the courts. Nevertheless, we believe that there has been a significant change in the attitude of the courts in recognizing the reality and severity of emotional suffering and the victims' right to compensation since Magruder made his observations more than 50 years ago. We would argue that emotional suffering and disability are as real as physical symptoms and disability. Undoubtedly, psychiatry and psychiatrists have been invaluable in changing the attitudes of the courts.

The distinction between the intentional and unintentional infliction of emotional harm is also very important. Nevertheless, in medical-legal assessments, unintentional emotional harm is far more common, as seen in the assessments of the emotional sequelae of motor vehicle accidents. In fact, one of us (B.F.H.) has completed 180 psychiatric assessments of litigants and has seen an intentional injury on only one occasion. Unintentional emotional harm is probably a more difficult concept for the nonpsychiatrist and the courts to grasp because of the absence of malice in the defendant, and yet the victims can have prolonged and severe symptoms that severely interfere with their lives.

In any case, we can be sure that psychiatrists will be asked to assess litigants more frequently to help the courts understand the emotional consequences of various physical and emotional injuries.

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Antidepressants and Cessation of Smoking

SIR: Neil B. Edwards, M.D., and associates (1) presented the potentially important finding that treatment with doxepin may facilitate efforts to cease smoking. They proposed that this occurs because of the amelioration of nicotine withdrawal symptoms. However, a clonidine patch should suffice (2) if this is the only benefit of the tricyclic. Maintenance of a nicotine-free state is more difficult than smoking cessation. Nicotine dependence, like other forms of substance abuse, is a condition with a high risk of relapse.

We propose that an antidepressant medication may do more than counteract withdrawal symptoms. There may be pharmacologic similarities in the actions of nicotine and antidepressants. Both alter the release of catecholamines in the CNS (3), and all antidepressant treatments studied to date (amitriptyline, desipramine, phenelzine, fluoxetine, bright artificial light, and lithium) alter the CNS hypothermic response to nicotine (4, 5).

Nicotine use and major depression may be associated. Some patients who do not ordinarily smoke claim that smoking decreases the intensity of their depressed mood. We hypothesize that, for people with even mild depression and decreased hedonic capacity, ceasing to smoke would be perceived as an unacceptable loss. Many patients report that they smoke more during psychiatric hospitalizations. We have observed, as have Dr. Edwards and colleagues (1), that some patients tend to crave nicotine-containing substances less when they are taking an antidepressant. Glassman et al. (2) recently reported that 61% of the smokers entering a smoking cessation program had a past history of major depression, even after persons with a current diagnosis of major depression were excluded. These individuals had significantly less success in discontinuing smoking for up to 4 weeks (33%) than did those without a past history of major depression (57%) ($p<0.05$). A past history of major depression predicted a poorer outcome.

We propose that an antidepressant may be useful not only as an adjunct in helping an individual stop smoking but also in maintaining abstinence. Dr. Edwards and his associates reported the status of their subjects 2 weeks after ceasing treatment with doxepin. The central effects of tricyclics may persist for a number of weeks after discontinuation. It is important to know whether the subjects relapsed and the time course of recidivism. We request that these data be provided. Future studies should compare the relapse rate of subjects continuing to take antidepressants with the relapse rate of subjects crossed over to an active placebo such as propantheline.

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STEPHEN F. PARISER, M.D.
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Drs. Edwards and Murphy Reply

SIR: We are acutely aware, as are Dr. Churchill and her associates, that maintenance of a nicotine-free state is more difficult than mere smoking cessation—that getting through nicotine withdrawal and achieving permanent abstinence are horses of quite different colors. However, we would contend that surviving withdrawal without relapse is a critical step toward permanent abstinence and that the easing of withdrawal symptoms, as we seem to have demonstrated with doxepin, may prove to be an important aid in this process. Whether or not our results in aiding short-term withdrawal are due only to amelioration of withdrawal symptoms is a vital, researchable question.

Dr. Churchill and colleagues suggest that the amelioration of withdrawal symptoms and the pharmacologic antidepressant effect of antidepressants are distinct phenomena. Our view is that these phenomena may be inextricably linked, that doxepin (and perhaps other antidepressants) ease withdrawal from nicotine precisely *because* they are antidepressants and *because* the antidepressants act on neurotransmitters in ways similar to that of nicotine. Because of its dose-dependent biphasic action on cholinergic receptors, nicotine can cause primary increases or decreases in CNS acetylcholine activity and also can cause the secondary release or inhibition of many other neurotransmitters, depending on the type of neuron activated, including acetylcholine itself, norepinephrine, serotonin, dopamine, and peptides (1). Many of these neurotransmitters are also affected by doxepin. Further, as noted in our study, there are distinct similarities between the clinical pictures of nicotine withdrawal and depression, and indeed, this fact was part of the impetus for our research. Whether or not clonidine would prove equally effective is also an important, researchable question that we intend to study.

The recently reported findings by Glassman et al. that clonidine aids in nicotine withdrawal and, further, that patients with histories of major depression were less successful in short-term cessation are indeed interesting. The finding that a history of major depression seems to predict poorer transit through the withdrawal period into short-term cessation might predict that doxepin or other antidepressants would do a better job.

We also agree with Dr. Churchill and associates that doxepin and/or other antidepressants might be helpful in maintaining abstinence. We anticipate that by the time these letters are published in the *Journal*, we will have presented our longer-term data at the annual meeting of the American Psychiatric Association; we also intend to publish these data. In any case, if doxepin and/or other antidepressants are to prove useful in maintenance, we predict that they will have to be given much longer than Dr. Churchill and associates suggest, perhaps for the majority of the year following nicotine cessation.

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Distinction Between Alzheimer's Disease and Primary Degenerative Dementia of the Alzheimer Type

SIR: A distinction is made in *DSM-III-R* between primary degenerative dementia of the Alzheimer type and Alzheimer's disease. The former is a clinical diagnosis, the latter a histological one.

It is true that making clinical diagnoses of primary degenerative dementia of the Alzheimer type according to *DSM-III* criteria will identify a group with a strong probability of having Alzheimer-type histological changes. This is very useful for some purposes. However, from such a group one will have excluded anyone who is not demented and who has symptoms not considered typical of Alzheimer's disease.

In their excellent article "Depression and Alzheimer's Disease," Barry W. Rovner, M.D., and his colleagues (1) were careful to state that they studied the prevalence of depression in a sample clinically diagnosed as having primary degenerative dementia of the Alzheimer type, but the title and abstract did not make the distinction between this and Alzheimer's disease. A patient who was depressed but not demented and who had Alzheimer's disease would have been excluded from their sample.

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PETER BIRKETT, M.D.
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Dr. Rovner Replies

SIR: Dr. Birkett correctly indicates that our study of depression and primary degenerative dementia of the Alzheimer type (a clinical diagnosis) excluded patients with Alzheimer's disease (a pathological diagnosis) who were not demented. We studied patients meeting the criteria for primary degenerative dementia of the Alzheimer type whose central psychopathological symptom was cognitive decline. Thus, our title and abstract would have been more accurate if we had used the clinical diagnosis rather than the pathological one.

The distinction raises an important issue. Clinical diagnoses such as probable Alzheimer's disease (NINCDS/ADRDA criteria) (1) and primary degenerative dementia of the Alzheimer type (*DSM-III-R* criteria) describe the dementia syndrome without qualification regarding neuropathology. Thus, these clinical criteria are tentative and subject to change as the natural history and pathology of Alzheimer's disease become better understood. For example, Kral (2) indicated that depression may precede dementia in patients who eventually develop Alzheimer's disease, much as affective disorder may precede dementia in Huntington's disease (3).

Longitudinal studies of depressed, nondemented elderly patients and patients at risk for Alzheimer's disease are needed to clarify these phenomena.

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Use of "Addictive" to Describe Neuroleptic Drugs

SIR: The word "addiction" stirs up emotion. It is a word that enters our practice in many settings: when treating a problem of drug abuse, when trying to prevent a problem of drug abuse, and when informing our patients, their families, and the general public about the abuse potential of the drugs we prescribe. It has become the job of the psychiatrist to clearly distinguish between and explain words such as "addiction," "tolerance," "withdrawal," and "dependence." The letter to the Editor from Peter R. Breggin, M.D. (1) blurred these boundaries in several important ways.

Dr. Breggin suggested that withdrawal symptoms associated with the discontinuation of neuroleptics are associated with "the difficulty we [clinicians] encounter in helping patients relinquish these drugs." Further, he stated that the definition of addiction as it appears in the 22nd edition of *Stedman's Medical Dictionary* supports the notion that those withdrawal symptoms may compel patients to continue ingesting neuroleptics. He suggested that we should acknowledge and label neuroleptics as potentially addictive.

There are several problems with drawing this conclusion. In citing the difficulty he encounters in helping patients discontinue neuroleptics, Dr. Breggin did not delineate the specific conditions of drug discontinuation. As with all psychotropics, the rate at which dosage is increased or decreased is quite important in terms of the effects produced. This is true for drugs that are not commonly abused as well as for those that are (2). Also, he seems to have lumped together the clinically distinct situations of tardive psychosis, withdrawal dyskinesia, and gastrointestinal upset. It is likely that they are distinct in terms of the mechanism of action (e.g., gastrointestinal upset caused by anticholinergic withdrawal, dyskinesia caused by a perturbation of the dopamine-acetylcholine activity ratio) and the psychological response associated with each (3). Finally, Dr. Breggin suggested the term "potentially addictive" for neuroleptics, but there are more precise terms available for the situations he described. Restarting neuroleptics for unexpected psychotic decompensation or nausea and vomiting is hardly the compulsive consumption of drugs that the word "addiction" usually refers to.

When one considers the host of adaptive and compensatory mechanisms which occur in most drug-organism interactions, it is clear that tolerance, rebound phenomena, and physiological dependence are the rule rather than the exception in pharmacotherapy (4, 5). Understanding them is the best way to guide our management of withdrawal syndromes, as when one attempts to reduce or discontinue neuroleptics. Including these syndromes in the group of addictions, either directly or by implication, serves only to cloud the important clinical issues for ourselves and our patients.

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SCOTT MCCORMICK, M.D.
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Dr. Breggin Replies

SIR: Dr. McCormick's response to my letter correctly observes that the word "addiction" stirs up emotion. It should! Many patients suffer such severe withdrawal symptoms that they feel compelled to continue taking neuroleptics, often despite painful side effects and the fear of tardive dyskinesia. By using the word "addiction," we will encourage ourselves and others to face the reality of how painfully difficult and even impossible withdrawal from these medications can be. In addition, as I described in my original letter, the problems associated with withdrawal from neuroleptics correspond exactly with the dictionary definition of addiction.

"Tolerance, rebound phenomena, and physiological dependence" may be the rule in pharmacotherapy, as Dr. McCormick suggests, but in regard to neuroleptics, the problems are sufficient to prevent many highly motivated patients from discontinuing these medications. They can feel overwhelmed by any one or several of the potential withdrawal symptoms: the mental symptoms of restlessness, agitation, anxiety, insomnia or sedation, loss of concentration, nightmares, or tardive psychosis; the embarrassing and sometimes painful and disabling dyskinesias; and the flu-like symptoms of nausea, vomiting, anorexia and weight loss, abdominal pains, headache, myalgia, paresthesias, rhinorrhea, alternating feelings of warmth and cold, diaphoresis, dizziness, malaise, and fatigue (1–3).

Dr. McCormick suggests that the withdrawal symptoms associated with neuroleptics are somehow related to "the specific conditions of drug discontinuation." Neuroleptic withdrawal phenomena should not be dismissed as dependent upon a particular clinician's approach or upon other circumstances. Neuroleptic withdrawal symptoms are well-documented, with dozens of relevant reports (2, 3).

Dr. McCormick suggests that I should not "lump together the clinically distinct situations of tardive psychosis, withdrawal dyskinesia, and gastrointestinal upset." However, they have important characteristics in common. First, all three are withdrawal phenomena that make it difficult and sometimes impossible for patients to stop taking neuroleptics. Second, all three are probably produced by the same basic CNS mechanism, the hyperactive rebound of one or more previously suppressed neurotransmitter systems.

Labeling the neuroleptics addictive does not "cloud the important clinical issues for ourselves and our patients." Instead, it shines a clarifying light on them. The addictive label emphasizes that patients must be warned about the difficulty of withdrawing from these drugs. It enables us to feel compassion toward our patients during the withdrawal process and encourages us to seek psychosocial and medical means for relieving their distress. It reminds us not to give up too quickly when the patient has trouble adjusting to lower levels of medication. It helps separate the patient's personal or psychiatric problems from those resulting from medication withdrawal, often relieving the patient of shame and confusion over the difficulty experienced in the withdrawal process. If the addictive label also encourages physicians to be more cautious in prescribing these dangerous medications (1), that is an advantage as well.

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PETER R. BREGGIN, M.D.
Bethesda, Md.

Clinical Differentiation Between Lethal Catatonia and Neuroleptic Malignant Syndrome

SIR: The description of the syndrome of lethal catatonia before the introduction of neuroleptics strongly supports the view that lethal catatonia and neuroleptic malignant syndrome are different conditions, a point that deserved further emphasis by Edgar Castillo, M.D., and colleagues in their article (1). The case of lethal catatonia described by the authors, however, did not manifest any classic catatonic symptoms, e.g., catatonic posturing with waxy flexibility, automatic obedience, negativism. It remains unclear, therefore, if this patient and some of the other cases described in the literature represent agitated psychoses of other types, including those of organic origin or manic excitement.

The authors did not provide convincing evidence for the argument that there are clear clinical differences between the two syndromes. The cardinal features of rigidity, autonomic instability, fever, excitement, and exhaustion can occur in both conditions. A review of the relevant cases in the literature does not suggest that there is predictable progression over time in either of the two conditions. Classification based on temporal stages (1) is likely to have limited clinical utility in differential diagnosis.

Dr. Castillo and associates recommended the use of neuroleptics in the treatment of lethal catatonia but failed to note that they are ineffective in controlling lethal catatonia in its full-blown form and that patients in advanced stages of lethal catatonia may worsen when taking neuroleptics (2). ECT may be the treatment of choice in lethal catatonia, particularly in the early stages (2). It also appears to be safe and effective in the treatment of neuroleptic malignant syndrome, particularly in the absence of cardiac arrhythmias (3, 4). Hence this treatment modality should be considered when the diagnosis remains unclear.

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D.P. DEVANAND, M.D.
New York, N.Y.

SIR: In their recent article Dr. Castillo and associates argued that lethal catatonia and neuroleptic malignant syndrome are different and in many cases should not be difficult to distinguish from each other. They pointed out that lethal catatonia often begins with extreme psychotic excitement, in contrast to neuroleptic malignant syndrome, which begins with severe extrapyramidally induced muscle rigidity. Early clinical differentiation is important because of differences in treatment. However, in some real-life cases, the distinction may be more difficult than the authors suggested. The patient with agitated catatonia usually has already received high doses of neuroleptics before an advanced stage is reached. Thus, if rigidity is present it may be difficult to know whether this represents neuroleptic malignant syndrome or, alternatively, neuroleptic-induced dystonia on top of lethal catatonia. On the other hand, Dr. Castillo and colleagues attributed certain symptoms (e.g., violent destructive behavior, hallucinations) to lethal catatonia but not to neuroleptic malignant syndrome, yet we might remain puzzled whether such symptoms in a particular case are due to lethal catatonia or the psychosis preceding neuroleptic malignant syndrome for which neuroleptics were originally used.

Differentiation between lethal catatonia and neuroleptic malignant syndrome is particularly a problem at a tertiary care hospital because the patient may be transferred there with incomplete records and an inadequate description of how the early symptoms progressed. While I agree that in theory clinicians ought to be able to distinguish the two syndromes by carefully considering how symptoms have evolved, unfortunately, we will continue to see many cases in which it remains very difficult to make the distinction.

JAMES L. LEVENSON, M.D.
Richmond, Va.

Dr. Rubin Replies

SIR: Drs. Devanand and Levenson raise several important issues about the differential diagnosis and treatment of lethal catatonia and neuroleptic malignant syndrome. Dr. Devanand highlights the imprecision of the term "lethal catatonia" on the basis of the absence of classic catatonic symptoms in some patients. My colleagues and I agree; the term was introduced by Stauder (1), and the case example we used, which Dr. Devanand states might be psychosis of a different type, was taken from the Stauder article. Obviously, only following death could a patient be categorized according to Stauder's appellation, and fewer cases of extreme psychotic excitement have a fatal outcome today than 55 years ago. The term "psychotic exhaustion syndrome" (2) more appropriately encompasses the range of symptoms and outcomes. Classification by stages is a fundamental method of description in medicine and, as we emphasized in our article (p. 325), was used "for illustrative purposes . . . [and] not meant to reflect a sharply defined sequence of events."

Dr. Levenson is correct that most patients with catatonic excitement receive neuroleptic treatment early on, which can complicate any attempt to distinguish a later stage of the "exhaustion syndrome" from neuroleptic malignant syndrome. He makes the very important point that tertiary care hospitals, in particular, may be faced with patients transferred in advanced stages of illness without adequate accompanying documentation of symptom progression or prior drug treatment, a situation we encounter repeatedly at our county hospital. This represents another among many examples that call for full disclosure of patient information between physicians and hospitals, especially in public sector psychiatry, where many of these cases are seen.

Finally, with regard to treatment, my coauthors and I respond to Dr. Devanand as follows. It is true that patients in advanced stages of lethal catatonia may worsen when taking neuroleptics (3), but how many of these represent incipient neuroleptic malignant syndrome where the prior drug history is not fully known (*vide supra*)? It is also true that ECT may be the treatment of choice in lethal catatonia, particularly in early stages (3), but for politicolegal reasons, here in California the use of ECT other than as a treatment of last resort is extremely difficult, particularly in public sector psychiatry. It is a moot point whether ECT is safe and effective in the treatment of neuroleptic malignant syndrome, particularly in the absence of cardiac arrythmias. ECT has been reported to be effective (4, 5), but the treatment itself can precipitate serious cardiac complications (4). Given the successes of dantrolene and bromocriptine in the management of neuroleptic malignant syndrome, one can argue against ECT as a front-line therapy.

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ROBERT T. RUBIN, M.D., PH.D.
Torrance, Calif.

Benzodiazepine Therapy and Withdrawal in Elderly Patients

SIR: The article by Edward Schweizer, M.D., and associates (1) reassuringly demonstrated the relative safety of withdrawing benzodiazepines according to a reasonable tapering schedule. However, it raised several important issues.

Although the authors described the sources of referral as physicians, self-referral, or notices in the local media, they did not identify the physician sources of referral by category (e.g., psychiatric versus primary care). It would have been most instructive if they had evaluated data such as 1) the referring physician's diagnosis in comparison with the research diagnosis, 2) the referring physician's original criteria for starting benzodiazepine therapy in comparison with psychiatric research standards, and 3) the reasons for which patients had not been withdrawn from the benzodiazepines they had been prescribed.

Other questions to be answered are 1) how do physicians in different categories compare in their use of short-acting as opposed to long-acting benzodiazepines, and 2) did the subjects feel they had been given adequate information by the prescribing physicians about the risks of maintenance treatment and of withdrawal? Although some subjects required reduction in the rate of tapering, the possibility that this was related to benzodiazepine half-life was not evaluated. Half-life may be an important factor in risk of withdrawal seizures (2) and other withdrawal phenomena.

The article also raised another essential problem. Not all subjects who had received benzodiazepines for a year or more required maintenance treatment. All the subjects' illnesses, such as major depressive disorder, could certainly have remitted within a year. During the therapy of these disorders, effort to taper the medication to test for remission or to lower the dosage would have been expected, yet some of the subjects were self-referred. As physicians, we must wonder how our patients perceive us if, indeed, they are unable to undergo safe withdrawal of medications without going through research protocols.

Apparently, use of benzodiazepines has become another source of political-economic abuse. When patients present with anxiety, the physician is faced with assisting them by means of thorough evaluation and treatment or by giving them the rapid "quick fix" afforded by benzodiazepines and so greatly rewarded by third-party reimbursement. Medicaid (and soon, Medicare) patients find that benzodiazepines can be obtained relatively free of charge, while psychotherapy is poorly reimbursed. This is true despite repeated evidence of the substantial risks of pharmacologic treatment (3, 4).

We psychiatrists must take the lead in educating both our professional colleagues and the public about appropriate use of psychotropic medications so that these can serve our patients' best interests. The article by Dr. Schweizer and associates encouraged safe withdrawal from benzodiazepines and thus was a step in the right direction.

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MICHAEL L. ZARR, M.D.
Flint, Mich.

Dr. Schweizer and Associates Reply

SIR: Dr. Zarr raises some important points with respect to the long-term use and discontinuation of benzodiazepines, some of which we cannot answer, while for others we have data available that are presently being prepared for further publications.

We have information on more than 250 chronic benzodiazepine-dependent patients regarding their initial diagnoses and the reasons for starting benzodiazepines. We used a timeline drug history, the Schedule for Affective Disorders—Lifetime Version (SADS-L), and diagnostic information from referring physicians when it was available. We also examined patient reports of symptom complaints at the time benzodiazepine therapy was first initiated. The as-yet unpublished data suggest the possibility that choice of a benzodiazepine for treatment may have been inappropriate in a substantial minority of cases.

We have no data indicating whether our subjects felt they had been given adequate information about the risk of maintenance benzodiazepine treatment. The whole issue of informed consent to treatment is clouded by the apparent low level of doctor-patient communication.

Dr. Zarr quite rightly questions whether most of our subjects suffered from illnesses that required more than one year of maintenance treatment. It is our position that most of these patients did not require long-term benzodiazepine therapy—certainly not continuously for many years. In fact, we have unpublished data which demonstrate that many patients, once they have been withdrawn from their maintenance benzodiazepines, show more improvement on clinical measures of anxiety and depression than they did during their chronically medicated state.

It is indeed correct that many physicians feel ill at ease with tapered withdrawal of a patient from benzodiazepines, particularly when the patient has been taking these drugs for many years. Also, physicians frequently do not find the time to spend on such a taper program, which admittedly can involve an inordinate amount of physicians' time.

Finally, Dr. Zarr points out that there may be social and economic pressures to prescribe benzodiazepines. We feel strongly that the proper translation of research findings into optimal clinical practice, and even social policy, is an important task. Unfortunately, the scope of our article, focusing as it did on benzodiazepine discontinuation, did not allow us to comment substantially on these issues of social policy.

EDWARD SCHWEIZER, M.D.
WARREN G. CASE, M.D.
KARL RICKELS, M.D.
Philadelphia, Pa.

Biochemical Basis for Schizophrenia

SIR: In the abstract of the article "Genetics and Psychiatry: Past Discoveries, Current Dilemmas, and Future Directions," Herbert Pardes, M.D., and associates (1) stated that "linked markers . . . have been reported for . . . schizophrenia." This assertion is not supported in the text of the article. I fear that the hope of Dr. Pardes and associates for a biochemical basis for schizophrenia, and thus a biochemical "cure," led them to be overly optimistic in the abstract. Otherwise, I found the article to be fairly well-balanced and appropriately hopeful.

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WILLIAM P. DRESCHER, M.D.
Lansing, Mich.

Dr. Pardes and Associates Reply

SIR: There are a number of molecular genetic studies that, building on earlier research in population genetics, suggest a role for inherited factors in schizophrenia. The two studies we cited (as references 35 and 36) were published in *Nature* in the fall of 1988. The first group of researchers (1) reported preliminary evidence for a susceptibility locus, in seven British and Icelandic families, on the proximal long arm of chromosome 5. The second (2) reported evidence against a locus in that chromosomal region in an extensive northern Swedish kindred.

Since those studies were published, other laboratories, including ours (3, 4), have also failed to replicate the positive findings. These conflicting results may reflect genetic heterogeneity, which characterizes many other complex human disorders (5), apparently including bipolar disorder and familial Alzheimer's disease. They may also reflect problems posed by the statistical analysis of disorders characterized by incomplete penetrance, variable expressivity, and an unknown mode of transmission.

Even if the exciting preliminary findings of linkage to a chromosome 5 locus are replicated, it will probably still take years of work to discover the gene, identify its product, and unravel the complex interaction between this biochemical vulnerability and environmental factors which produces the scourge that is schizophrenia.

Nevertheless, molecular genetics has made a critical contribution to the discovery of the genes for a number of disorders, including Duchenne's muscular dystrophy. Thus, we feel it is fair to take a posture of guarded optimism toward the likelihood that this approach will contribute to the understanding of the mental illnesses.

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Reprints of letters to the Editor are not available.

Position Statement on Psychiatric Services in Jails and Prisons

This statement was prepared by the Task Force on Psychiatric Services in Jails and Prisons[1] *of the Council on Psychiatric Services. It was approved by the Assembly in November 1988 and by the Board of Trustees in December 1988.*

The American Psychiatric Association accords a high priority to the care and treatment of patients from groups that are underserved, especially groups that lack strong political constituencies. Such groups include the chronically mentally ill and the mentally ill homeless. Also included, but less visible, are the mentally ill in jails and prisons.

The mentally ill are especially vulnerable to the difficult conditions that typically prevail in our jails and prisons. Psychiatrists practicing in such facilities attempt to provide adequate services under the most difficult working circumstances, with inadequate professional recognition and remuneration, and, perhaps most burdensome of all, in the midst of frequently deplorable conditions.

In the 1974 "Position Statement on Medical and Psychiatric Care in Correctional Institutions" (1), APA called for a "full range of . . . psychiatric services" in jails and prisons. Noting that "an essential part of a minimal medical care delivery system consists of the early detection, diagnosis, treatment, and prevention of psychiatric illness," the APA position statement went on to forcefully state that "the fact of incarceration imposes upon public authority the special duty to provide adequate medical services, including psychiatric services. Availability of such services is and should be a right of the incarcerated individual."

However, a decade later, in 1983, APA was obliged to observe that "providing mental health treatment for persons in jails and prisons has, over the years, proved a refractory problem" (2). In part, this situation persists because of the altered social context of the operations of correctional facilities, which has resulted in tightened admission criteria for psychiatric hospitalization, fewer beds, limits on length of stay, reduced availability and use of civil commitments, and changing sentencing practices that have increased the number of inmates needing mental health services. Legislative demands for fiscal austerity and associated public policies, such as deinstitutionalization, have led to a complex set of circumstances that have been associated with an increase in the number of mentally ill persons who are at risk of incarceration in local jails because of minor charges used to address their disturbed behavior. This situation has resulted in a substantial increase in the population of inmates requiring mental health care.

Severe overcrowding is an additional factor often contributing to the inadequacy of psychiatric services in jails and prisons. Conditions are often so bad in contemporary jails and prisons that both state and federal courts have mandated sweeping changes in their operations. The Supreme Court has ruled that it is the obligation of correctional officials to ensure that the civil rights of the mentally ill are protected. This obligation includes the right to adequate mental health care. Providing adequate mental health care in this context rests on the following principles:

1. The fundamental goal of a mental health service should be to provide the same level of care to patients in the criminal justice process that is available in the community.
2. The effective delivery of mental health services in correctional settings requires that there be a balance between security and treatment needs. There is no inherent conflict between security and treatment.
3. A therapeutic environment can be created in a jail or a prison setting if there is clinical leadership, with authority to create such an environment.
4. Timely and effective access to mental health treatment is a hallmark of adequate mental health care. Necessary staffing levels should be determined by what is essential to ensure that access.
5. Psychiatrists should take a leadership role administratively as well as clinically. Further, it is imperative that psychiatrists define their professional responsibilities to include advocacy for improving mental health services in jails and prisons.
6. Psychiatrists should actively oppose discrimination based on religion, race, ethnic background, or sexual preference, not only for mental health services but for all activities in the judicial-legal process.

Elaborations and explications of these principles can be found in the report of the Task Force on Psychiatric Services in Jails and Prisons, June 1988, which will be available from the APA Office of Psychiatric Services in the near future.

Finally, APA calls on its members to participate in the care and treatment of the mentally ill in jails and prisons, for without an increased commitment and involvement of its membership in providing services to the mentally ill in jails and prisons, position statements such as this will be meaningless. The breadth and depth of these problems demand much more.

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[1] The task force included Henry C. Weinstein, M.D. (chairperson and Assembly liaison), James O. Hoover, M.D., Jeffrey L. Metzner, M.D., Robert L. Sadoff, M.D., Veva H. Zimmerman, M.D., and Bruce Kagan, M.D. (APA/Burroughs Wellcome Fellow). Consultants to the task force were Saleem A. Shah, Ph.D., Henry J. Steadman, Ph.D., Rachel Ehrenfeld, Ph.D., and Susan O. Reed, M.P.A.

Highlights of the 142nd Annual Meeting

The 142nd annual meeting of the American Psychiatric Association was held in San Francisco, California, May 6–11, 1989. The total registration was 15,093, including 8,261 members; 2,243 spouses, other family members, and guests; 2,866 nonmembers; 1,375 exhibitors; 213 members of the media; and 135 staff members.

Opening Session

The opening session was called to order by Paul J. Fink, M.D., 117th President of the Association, on Sunday evening, May 7, in the Moscone Convention Center. Dr. Fink read a letter of greetings from the Honorable Art Agnos, Mayor of the City of San Francisco, and one from the Honorable George Deukmejian, Governor of the State of California. Dr. Fink then introduced Dr. David Werdegar, Director of the Department of Public Health, City and County of San Francisco.

Dr. Fink recognized members of the APA Board of Trustees; members of the APA Assembly; past Presidents; past Speakers of the Assembly; past Vice-Presidents of the Association; newly elected national officers, trustees, and Assembly officers; presidents of APA district branches; chairpersons of APA councils, commissions and joint commissions; and the APA Medical Director.

Allan Tasman, M.D., chairperson of the Scientific Program Committee, and Kathleen Bell Unger, M.D., and Mel I. Blaustein, M.D., co-chairpersons of the Local Arrangements Committee, were introduced and thanked by Dr. Fink.

Dr. Fink then introduced the following distinguished representatives of psychiatric and other related organizations from the United States and abroad:

International Scholars: Prof. Franco Ferracuti of Italy; Prof. Mogens Schou of Denmark; Prof. F. Lieh Mak of Hong Kong; and Dr. Anthony Storr of England.

Representatives of Other International Organizations and Psychiatric Associations in Other Countries: Dr. Jorge Alberto Costa e Silva, Inter-American Council of Psychiatric Organizations, World Psychiatric Association, and World Association for Social Psychiatry; Dr. Rodolfo Fahrer, Argentine Society of Consultation-Liaison Psychiatry; Dr. Joan Lawrence, Royal Australian and New Zealand College of Psychiatrists; Prof. Dr. Hartmann Hinterhuber, Austrian Society of Psychiatry and Neurology; Dr. Otto Doerr, Chilean Society of Psychiatry and Neurology; Dr. Joachim Knop, Danish Psychiatric Society; Dr. Carlos Leon, Ecuadorian Psychiatric Association; Dr. Kari Pylkkanen, Finnish Psychiatric Association; Dr. Annie Fuster, French Association of Psychiatrists in Private Practice; Dr. Johannes Meyer-Lindenberg, German Society of Psychiatry and Mental Diseases; Dr. George N. Christodoulou, Greek Psychiatric Association; Dr. Augusto Aguilera, Psychiatric Association of Guatemala; Dr. C.M. Chung, Hong Kong Psychiatric Association; Dr. Helga Hannesdottir, Icelandic Psychiatric Association; Dr. Satoshi Shikiba, Japanese Association of Psychiatric Hospitals; Dr. Shiroe Miura, Japanese Society for Psychiatry and Neurology; Dr. Chung-Kyoon Lee, Korean Neuropsychiatric Association; Dr. J.R. de la Fuente, Mexican Psychiatric Association; Prof. Dr. W.J. Schudel, Netherlands Psychiatric Association; Dr. S. Haroon Ahmed, Pakistan Psychiatric Society; Dr. Michal Wroniszewski, Polish Psychiatric Association; Dr. Ming-Been Lee, Taiwan Society of Psychiatry; Dr. J.L.T. Birley, Royal College of Psychiatrists of the United Kingdom; Dr. Enrique Probst Dinerstein, Uruguayan Psychiatric Society; Dr. Ruben Hernandez Serrano, Venezuelan Medical Federation; Dr. Antonio Pacheco Hernandez, Venezuelan Psychiatric Association.

Representatives of organizations in the United States: Dr. Renato R. Alcalde, President, Philippine Psychiatrists in America; Dr. Jambur Ananth, President, American Association of Psychiatrists from India; Dr. Nancy C. Andreasen, President, American Psychopathological Association; Dr. Harry Babikian, President, American Academy of Psychoanalysis; Dr. Oliver H. Beahrs, President, American College of Surgeons; Dr. Sheila Blume, Past-President, American Medical Society on Alcoholism and Other Drug Dependencies, Inc.; Dr. Carl C. Bell, Representative, National Council of Community Mental Health Centers; Dr. Floyd E. Bloom, President, American College of Neuropsychopharmacology; Dr. Roger Boles, Representative, American Academy of Otolaryngology—Head & Neck Surgery; Dr. Majorie Braude, Regional Governor, American Medical Women's Association, Inc.; Mrs. Zoe Brunt, President, American Psychiatric Association Auxiliary; Dr. Ewald W. Busse, President, International Association of Gerontology; Dr. Robert J. Campbell III, President, American Association of Psychiatric Administrators; Dr. Sara Charles, Representative, Council of Medical Specialty Societies; Dr. Thomas K. Ciesla, President, National Guild of Catholic Psychiatrists; Reverend Victoria Brannan Cowell, President, Association of Mental Health Clergy; Dr. Homer C. Curtis, President, American Psychoanalytic Association; Dr. Leah J. Dickstein, President, Association of Women Psychiatrists; Ms. Suzanne Dworak-Peck, President, National Association of Social Workers, Inc.; Dr. Norbert Enzer, President, Society of Professors of Child and Adolescent Psychiatry; Dr. Paul Errera, Director, Mental Health and Behavioral Sciences, Veterans Administration; Dr. Shervert H. Frazier, President, Benjamin Rush Society; Dr. D. Ray Freebury, President, Canadian Psychoanalytic Society; Ms. Carol W. Garvin, President, National Mental Health Association; Dr. Naomi Goldstein, President, American Board of Forensic Psychiatry, Inc.; Dr. Frederick K. Goodwin, Administrator, Alcohol, Drug Abuse and Mental Health Administration; Dr. Enoch Gordis, Director, National Institute on Alcohol Abuse and Alcoholism; Dr. A. Dale Gulledge, President, Academy of Psychosomatic Medicine; Dr. Thelissa Harris, President-Elect, Black Psychiatrists of America; Mr. Hal Hollister, Executive Director, National Alliance for Research on Schizophrenia and Depression; Dr. Thomas Horvath, President, National Association of Veterans Administration Chiefs of Psychiatry; Ms. Artie Houston, President, National Depressive and Manic Depressive Association; Dr. Syed Arshad Husain, President, Pakistan Psychiatric Society of America; Dr. Kazimierz Jankowski, President, Association of Polish Psychiatrists and Neurologists in America; Dr. Ali Jarrahi, President, Society of Iranian Psychiatrists in North America; Mr. Dennis R. Jones, President, National Association of State Mental Health Program Directors; Dr. Ferdinand Jones, President, American Orthopsychiatric Association; Dr. Philip Katz, President, American Society for Adolescent Psychiatry; Dr. Jerald Kay, President, American Association of Directors of Psychiatric Residency Training, Inc.; Dr. David J. Kupfer, President, Society of Biological Psychiatry; Dr. Lawrence W. Lazarus, President, American Association for Geriatric Psychiatry; Dr. Leo Madow, President, American College of Psychoanalysts; Dr. M.J. Martin, President, American Board of Psychiatry and Neurology, Inc. and of the American College of Psychiatrists; Dr. Robert E. McAfee, Member, Board of Trustees, American Medical Association; Dr. Sheldon I. Miller, President, American Academy of Psychiatrists in Alcoholism and Addictions; Dr. Henry Nasrallah, Vice-President, American Academy of Clinical Psychiatrists; Ms. Patricia Pothier, Acting Dean & Professor, American Nurses' Association; Dr. John Racy, President, Association of Directors of Medical Student Education in Psychiatry; Dr. James Randall, President, American Society of Psychoanalytic Physicians; Dr. William H. Reid, President-Elect, American Academy of Psychiatry and the Law; Mr. Donald Richardson, Immediate Past-President, National Alliance for the Mentally Ill; Dr. Carolyn B. Robinowitz, President, Group for the Advancement of Psychiatry; Dr. Hugh M. Sampath, President, Canadian Psychiatric Association; Dr. Stephen C. Scheiber, President, Association for Academic Psychiatry; Dr. Charles R. Schuster, Director, National Institute on Drug Abuse; Dr. Walter W. Shervington, National Medical Association; Mr. Loren B. Shook, President, National Association of Private Psychiatric Hospitals; Dr. James H. Shore, President, American Association of Chairmen of Departments of Psychiatry; Dr. Melvin J. Stern, Representative, American Group Psychotherapy Association; Dr. Ellen Taliaferro, Vice-President, American College of Emergency Physicians; Dr. Mahmoud S. Taman, President, Arab American Psychiatrists Association of America; Dr. Clifton Tennison, Vice-President, American Association of Community Psychiatrists; Dr. Reiko Homma True, Deputy Director of Health for Mental Health, Substance Abuse and Forensic Services, Department of Public Health, City and County of San Francisco; Dr. Eduardo R. Val, President, American Society of Hispanic Psychiatrists; Dr. Adnan Varol, President, Turkish-American Neuropsychiatric Association; Dr. Harold M. Visotsky, President, American Association for Social Psychiatry; Dr. Jerry M. Wiener, President, American Academy of Child and Adolescent Psychiatry; Dr. John C. Wolfe, President, American College of Mental Health Administration.

Carolyn B. Robinowitz, M.D., introduced Dr. Fink, who gave the Presidential Address, "On Being Ethical in an Unethical World" (printed elsewhere in this issue of the *Journal*). Jack D. Barchas, M.D., introduced Herbert Pardes, M.D., President-Elect of the Association, who gave the Response to the Presidential Address, "The Research Alliance: Road to Clinical Excellence" (printed elsewhere in this issue). Dr. Fink then adjourned the opening session.

Business Meeting

The annual business meeting was called to order by Paul J. Fink, M.D., in the Moscone Convention Center on Monday, May 8, 1989, at 12:30 p.m.

First session. Edward Hanin, M.D., Recorder, called the roll of the Assembly representatives and announced the presence of a quorum. Dr. John S. McIntyre, Speaker, spoke in tribute to James C. Johnson, Jr., M.D. (1920–1988) and William R. Sorum, M.D. (1922–1988), and then asked the audience to observe a moment of silence in memory of all members and Fellows who died during the past year. Edward C. Kirby, Jr., M.D., chairperson of the Committee of Tellers, announced the results of the election of officers and Trustees. The reports to the membership followed. Elissa P. Benedek, M.D., presented the Secretary's report, which was followed by the reports of Alan I. Levenson, M.D., Treasurer; John S. McIntyre, M.D., Speaker of the Assembly; Gerald H. Flamm, M.D., Speaker-Elect of the Assembly; Richard Thurrell, M.D., member of the Committee on the Constitution and By-Laws; and Michael J. Vergare, M.D., chairperson of the Membership Committee. Melvin Sabshin, M.D., presented the Medical Director's report. Reports of all the councils were also available. All reports were accepted by the membership as submitted and will be published in the October 1989 issue of the *American Journal of Psychiatry.*

Dr. Thurrell also read for the membership a proposed amendment to Chapter 3 of the APA By-Laws which would allow the Speaker-Elect to exercise the Speaker's vote on the Board of Trustees when the Speaker is absent. This amendment will be placed on the 1990 ballot for consideration by the membership.

Dr. Fink presented the Speaker's plaque to John S. McIntyre, M.D., retiring Speaker, and the Vice-President's badge to Allan Beigel, M.D., retiring Vice-President. Melvin Sabshin, M.D., presented the President's badge to Dr. Fink. Dr. Fink then recessed the first session of the business meeting.

Second Session. Following the business meeting Dr. Fink called the Annual Forum for all voting members to order. The issues discussed on the floor included: whether emphasis on advances in research will eclipse patient care issues, whether the industry sponsored symposia receive too much visibility in the program, the low attendance at the business meeting, what assistance is being provided to victims in Armenia (the APA has offered assistance to the State Department), and the ongoing problems of continuity of care in the public mental health sector.

The business meeting was then adjourned by Dr. Fink.

Convocation

The 33rd Convocation of Fellows was held in the San Francisco Hilton beginning at 8:00 p.m. on Monday, May 8. Dr. Fink presided. After the processional march, Dr. Fink called the Convocation to order. The invocation was given by Rabbi David Davis. President-Elect Herbert Pardes, M.D., then led the ceremony conferring Life Fellowship and the induction of Fellows of the Association. Dr. Fink read the names of the 1988 Corresponding Fellows: Manuilal Talakshi Gada, M.D., Bombay, India; Itzhak Levav, M.D., Jerusalem, Israel; Roger Maximiliano Montenegro, M.D., Buenos Aires, Argentina; Roshan Lal Narang, M.D., Ludhiana, India; Enrique Probst Dinerstein, M.D., Montevideo, Uruguay; George Gregory C. Rwegellera, M.D., Geneva, Switzerland; and Jag Mohan Wadhawan, M.D., Assan, India. The following 50-year Life Fellows and Life Members (1939–1989) were then recognized: Lewis Barbato, M.D., Denver, CO; Margaret D. Barber, M.D., North Miami, FL; Harvey Bartle, Jr., M.D., Bryn Mawr, PA; Sam Beanstock, M.D., San Antonio, TX; Newton J.T. Bigelow, M.D., Marcy, NY; Roy Everett Bingham, M.D., Jeffersontown, KY; Richard F. Binzley, M.D., Shaker Heights, OH; Rex Blankinship, M.D., Richmond, VA; Norman Q. Brill, M.D., Los Angeles, CA; Henry W. Brosin, M.D., Tucson, AZ; Howard R. Campbell, M.D., Dayton, OH; Louis S. Chase, M.D., Waban, MA; William Corwin, M.D., Ocala, FL; Murray A. Diamond, M.D., New Orleans, LA; Donald R. Easton, M.D., Edmonton, AB, Canada; Jule Eisenbud, M.D., Denver, CO; Eugene A. Eisner, M.D., Scarsdale, NY; John Westley Evans, M.D., Otter Rock, OR; Jack R. Ewalt, M.D., Tucson, AZ; Hyman H. Fingert, M.D., St. Louis, MO; Hamilton F. Ford, M.D., Galveston, TX; Frances H. Gitelson, M.D., Palo Alto, CA; Henry G. Grand, M.D., New York, NY; Maurice Grossman, M.D., Palo Alto, CA; Martin Grotjahn, M.D., Los Angeles, CA; Werner Hamburger, M.D., Atlantic City, NJ; Edward E. Harkavy, M.D., Larchmont, NY; William L. Holt, M.D., Feura Bush, NY; Morris Isenberg, M.D., Forest Hills, NY; Richard L. Jenkins, M.D., Iowa City, IA; Maurice Kaplan, M.D., Highland Park, IL; Luisa Kerschbaumer, M.D., Willard, NY; Harry L. Kozol, M.D., Boston, MA; Edward E. Landis, M.D., Anchorage, KY; Leonard C. Lang, M.D., Delmar, NY; David W. Lester, M.D., San Diego, CA; Norman A. Levy, M.D., Santa Monica, CA; Frank A. Majka, M.D., Milwaukee, WI; Judd Marmor, M.D., Los Angeles, CA; Aaron S. Mason, M.D., Lexington, KY; Marjorie C. Meehan, M.D., Chicago, IL; Ronald B. Mershon, M.D., Fairhope, AL; Walter L. Moore, M.D., St. Charles, MO; Lillian G. Moulton, M.D., Evansville, IN; Ethel E.H. O'Brien, M.D., Louisville, KY; Joseph W. Owen, M.D., Riverdale, NY; Joseph Pessin, M.D., Burbank, CA; Marvin R. Plesset, M.D., Pittsburgh, PA; William R. Purmort, Jr., M.D., Camarillo, CA; Chester L. Reynolds, M.D., El Paso, TX; William D. Rogers, M.D., Chattahoochee, FL; John Romano, M.D., Rochester, NY; Mabel Ross, M.D., Sun City, AZ; Emanuel Rubin, M.D., North Miami Beach, FL; Hyman S. Rubinstein, M.D., Baltimore, MD; Samuel H. Ruskin, M.D., Southfield, MI; Maurice A. Schiller, M.D., Chicago, IL; Louis B. Shapiro, M.D., Chicago, IL; John R. Shawver, M.D., Albuquerque, NM; Alexander Simon, M.D., San Francisco, CA; Leo Stone, M.D., New York, NY; Perry C. Talkington, M.D., Dallas, TX; Anna C. Todd, M.D., St. Petersburg, FL; William J. Turner, M.D., Northport, NY; James N. Williams, M.D., Virginia Beach, VA; Benjamin Wintrob, M.D., Toronto, ON, Canada; Joseph Wortis, M.D., Brooklyn, NY; Bascom B. Young, M.D., Stuart, FL; and William G. Young, M.D., North Ferrisburg, VT.

Special Presidential Commendations were presented to Shervert Frazier, M.D., "in recognition of his contributions to research, education and clinical care"; to Mr. Michael Unhjem, 1988 National President of the NMHA, "in appreciation of his enormous and vital contributions to the battle against stigma experienced by the mentally ill"; to Mr. Darrell Sifford, Columnist, *Philadelphia Inquirer*, "in appreciation of his enormous and vital contributions to the battle against stigma experienced by the mentally ill"; to Senator Pete Domenici (R-NM) and his wife Nancy, "in appreciation of their enormous and vital contributions to the battle against stigma experienced by the mentally ill"; and to Former First Lady Rosalynn Carter, "in appreciation of her enormous and vital contributions to the battle against stigma experienced by the mentally ill."

Dr. Fink introduced Mrs. Kitty Dukakis, the First Lady of Massachusetts and wife of Democratic Nominee Michael Dukakis. Mrs. Dukakis emerged from the 1988 Presidential Campaign as one of its bright stars, traveling hundreds of thousands of miles across America on behalf of her husband's quest for the Presidency. She courageously told Americans of her 26-year dependency on diet pills; spoke passionately about an America that can provide for its most vulnerable; and learned first-hand, during her extraordinary journey, of the strength and complexity of all that is America. Kitty Dukakis gave the William C. Menninger Memorial Convocation Lecture, "The Stigma of Substance Abuse."

After introducing the chairpersons of the award committees, Dr. Fink presented the 1989 awards. Distinguished Service Awards were presented by Dr. Fink to Eric R. Kandel, M.D., a university professor at the Center for Neurobiology and Behavior of the College of Physicians and Surgeons of Columbia University and a senior investigator at the Howard Hughes Medical Institute; to Solomon H. Snyder, M.D., director of the department of neuroscience and Distinguished Service Professor of Neuroscience, Pharmacology and Psychiatry at Johns Hopkins; to the American Association of Chairmen of Departments of Psychiatry; and to the Robert Wood Johnson Foundation. This award was established by the Board of Trustees to honor APA members whose distinguished careers have ennobled the profession of psychiatry and associations which have contributed greatly to the American Psychiatric Association and its work.

Roger Peele, M.D., chairman of the psychiatry department, chief clinical officer, and director of the office of training and standards for the Washington, D.C. Commission on Mental Health Services, received the Administrative Psychiatry Award. This award honors an APA member who is a nationally recognized clinician executive, whose effectiveness as an administrator of major mental health programs has expanded the body of knowledge of management in the mental health services delivery system, and whose effectiveness has made it possible for them to function as a role model for other psychiatrists.

The APA/Dista Products Resident Research Award, established in 1988 to honor a psychiatry resident for excellence in research undertaken during residency, was presented to Lisa Dixon, M.D., a resident-in-training at Payne Whitney Clinic in New York, and to James H. Meador-Woodruff, M.D., a resident-in-training in the department of psychiatry at the University of Michigan.

Kitty Dukakis, the First Lady of Massachusetts, was the recipient of the first Award for Patient Advocacy, established in 1988 to recognize a public figure respected for personal accomplishments and beliefs, who has promoted the improvement of services for people coping with mental disorders and substance abuse, and who has fought stigma by speaking out about experiences with mental illness and psychiatric treatment.

The Foundations' Fund Prize for Research in Psychiatry, established to recognize outstanding research in psychiatry and its basic sciences, was awarded to Alexander H. Glassman, M.D., chief of clinical psychopharmacology at New York State Psychiatric Institute and professor of psychiatry at the College of Physicians and Surgeons of Columbia University, and to Philip W. Gold, M.D., chief of the clinical neuroendocrinology branch in the NIMH Intramural Research Program.

The Samuel G. Hibbs Award was presented to Hagop S. Akiskal, M.D., professor of psychiatry and director of the section of affective disorders at the University of Tennessee in Memphis. This award is given for the best unpublished paper on a clinical subject.

The Blanche F. Ittleson Award for Research in Child Psychiatry, given to a child psychiatrist or group of investigators for published results of research pertaining to the mental health of children, was presented to Javad H. Kashani, M.D., director of child and adolescent services and professor of psychiatry, pediatrics, and medicine at the University of Missouri, Columbia.

The first two Kempf Fund Awards for Research Development in Psychobiological Psychiatry were presented to Lawrence A. Dunn, M.D., associate in psychiatry at Duke University Medical Center, to honor a resident who demonstrates exceptional promise in psychiatric research; and to Charles B. Nemeroff, M.D., associate professor of psychiatry, pharmacology and neurobiology and chief of the division of biological psychiatry at Duke University, to honor research excellence in the psychobiological, psychological, and/or sociological causes and treatment for the mental disease known as schizophrenia.

Jeanne Spurlock, M.D., deputy medical director of the American Psychiatric Association, received the Agnes Purcell McGavin Award, given to honor a psychiatrist who has done and is currently doing outstanding work related to the preventive aspects of the emotional disorders of childhood.

The Robert T. Morse Writers Award, which honors popular writers who have made major contributions to the public understanding of psychiatry and mental illness, was presented to Mr. Ronald Kotulak, science writer for *The Chicago Tribune*.

William W. Meissner, M.D., university professor of psychoanalysis at Boston College and training and supervising analyst at the Boston Psychoanalytic Institute, received the Oskar Pfister Award, given to honor outstanding contributions in the field of psychiatry and religion.

The Psychiatric Institutes of America Foundation Award for Research Development in Hospital Psychiatry, given to honor outstanding contributions in hospital psychiatry research, was presented to Alexis A. Giese, M.D., instructor in the department of psychiatry at Georgetown University and medical director of its Psychiatry Day Treatment Center, and to Thomas N. Wise, M.D., chairman of the department of psychiatry at Fairfax Hospital in Fairfax, Virginia.

The Robert L. Robinson Award, which recognizes radio and television (including cable) productions that contribute significantly to a better public understanding of psychiatry and mental illness, was given to journalist Bill Kurtis, co-anchor of WBBM-CBS TV "The Five O'Clock News" and "The Ten O'Clock News," and to Harvey L. Ruben, M.D., host of "Talknet," a three-hour mental health issues call-in show on the NBC Radio Network.

The Arnold L. van Ameringen Award in Psychiatric Rehabilitation was presented to Robert P. Liberman, M.D., professor of psychiatry at UCLA School of Medicine and chief of the rehabilitation service at the Brentwood Division of the West Los Angeles VA Medical Center, for his outstanding contribution to the field of psychiatric rehabilitation, in the areas of service, research, education, advocacy, or a combination thereof.

Walter Weintraub, M.D., professor and director of graduate education in the department of psychiatry at the University of Maryland School of Medicine, was given the Seymour D. Vestermark Award, which recognizes an educator who has made outstanding contributions to undergraduate, graduate, or postgraduate education and career development in psychiatry.

The Jack Weinberg Memorial Award for Geriatric Psychiatry was presented to Robert N. Butler, M.D., Brookdale Professor and chairman of the Gerald and Mary Ellen Ritter Department of Geriatrics and Adult Development of Mount Sinai Medical Center. This award honors a psychiatrist who has demonstrated special leadership or who has done outstanding work in clinical practice, training, or research into geriatric psychiatry anywhere in the world.

After the presentation of these awards, Dr. Fink adjourned the Convocation.

Awards presented at meetings other than the Convocation included the following:

District Branch Newsletter of the Year Awards were presented to the *Connecticut Psychiatrist*, Boris Rifkin, M.D., Editor, and *The Central New York District Branch Newsletter*, Mokarram H. Jafri, M.D., Editor; and awards for continuing excellence to the *Florida Psychiatric Society Newsletter*, Richard E. Gordon, M.D., Editor; *The Washington Psychiatric Society Newsletter*, Geraldine Schaeffer, M.D., Editor; and the *Nebraska Newsletter*, Beverly T. Mead, M.D., Editor.

The Manfred S. Guttmacher Award, given to honor outstanding contributions to the literature of forensic psychiatry, was given to Robert D. Miller, M.D., training director at the Mendota Forensic Center in Madison, Wisconsin.

The first Lilly Psychiatric Research Fellowship was presented to James H. Meador-Woodruff, M.D., currently completing a residency in psychiatry at the University of Michigan. The fellowship was established to provide support for the career development of a postgraduate medical trainee who has shown exceptional promise in psychiatric research.

The Jacob K. Javits Public Service Award, which honors a public servant who has made a significant contribution to the cause of the mentally ill, was received by The Honorable Silvio O. Conte (R-MA).

Scientific Sessions

The Scientific Program began on Monday, May 8, but Continuing Medical Education (CME) courses and industry sponsored symposia began on Saturday, May 6. There were 12 discussion groups, three forums, 129 symposia, 24 industry sponsored symposia, 422 new research presentations, three scientific debates, 144 papers presented in 48 paper sessions, 133 workshops (including 36 APA component presentations), 15 film sessions, 58 videotapes and three video production clinics, 96 CME courses, four medical updates, five review of psychiatry sessions, four clinical case conferences, two continuous clinical case conferences, two "research consultations with . . .," and six "clinical consultations with . . . ." Other sessions included "Research Advances in Psychiatry: An Update for the Clinician"; "Workshops on Private Practice Issues"; the residents' session, "Meet the Experts: Sunny-Side Up"; "Patients, Consumers, and Their Families: An Open Forum"; an NIMH workshop; the public symposium; a Social Security workshop; and an AIDS program and resource center.

There were 27 lectures. The speakers, their current positions, and the titles of their presentation are listed here.

On Monday, May 8, the following speakers gave lectures: Anthony Storr, M.B., psychiatrist, noted author and an emeritus fellow of Green College, Oxford, England, "Solitude and Creativity"; Itzhak Levav, M.D., regional advisor in mental health for the WHO/PAHO, the Simon Bolivar Award Lecture, "Mental Health in the Americas: Challenges and Responses"; Robert J. Stoller, M.D., professor of psychiatry, University of California, Los Angeles, School of Medicine, "Overcoming Stigma: Do Psychiatrists Shrink From the Study of Erotics?"; Afaf M. Mahfouz, Ph.D., psychoanalyst, international legal scholar and associate professor in the School of Commerce and Business at Helwan University in Cairo, "Women in Islam: Images, Myths and Perceptions"; Prof. Mogens Schou, professor of psychiatry (biological psychiatry and psychopharmacology) at Aarhus University, "Relapse Prevention in Manic-Depressive Illness: What Is Important and What Is Not?"; and John Romano, M.D., professor emeritus, University of Rochester School of Medicine and Dentistry, "Reminiscences: 1938 and Since."

On Tuesday, May 9, the following lectures were given: Melvin Sabshin, M.D., Medical Director of the APA, the Adolf Meyer Award Lecture, "Turning Points in Twentieth Century American Psychiatry"; James F. Gusella, Ph.D., director of the Neurogenetics Laboratory at Massachusetts General Hospital, "DNA Markers in Neuropsychiatric Disease"; Tony Brown, journalist, producer, educator, and film director, the Solomon Carter Fuller Award Lecture, "A Plan for the 90's"; F. Lieh Mak, M.D., professor and head of the department of psychiatry at the University of Hong Kong, "Chinese Culture and Psychiatry: The Emperor's New Clothes"; Eugene Garfield, Ph.D., founder, president, and chief executive officer of the Institute for Scientific Information, "The Impact of Psychiatry on the World of Research"; Anna Ornstein, M.D., professor of child psychiatry at the University of Cincinnati, "The Curative Fantasy and Psychic Recovery"; Lewis L. Judd, M.D., Director, NIMH, "A National Mental Health Agenda: Psychiatry's Role"; Prof. Franco Ferracuti, professor of criminological medicine and forensic psychiatry, University of Rome, "Psychiatric Aspects of Terrorism"; and Ching-piao Chien, M.D., professor of psychiatry at the Neuropsychiatric Institute and Hospital of the University of California, Los Angeles, "Culture, Ethnicity and Psychopharmacology."

On Wednesday, May 10, the following lectures were presented: Walter Weintraub, M.D., professor and director of graduate education in the department of psychiatry at the University of Maryland School of Medicine, the Seymour D. Vestermark Award Lecture, "Public Sector Psychiatrists: Crusaders or Careerists?"; Seymour Reichlin, M.D., chief of endocrinology at the New England Medical Center and director of the General Clinical Research Center, Tufts–New England Medical Center in Boston, "Neuroendocrinology, Brain and Behavior: Evolving Concepts"; Robert W. Gibson, M.D., president and chief executive officer of the Sheppard and Enoch Pratt Hospital in Baltimore, "The Psychiatric Hospital: Cause or Solution of Stigma?"; Guenter B. Risse, M.D., professor and chairman, department of history of health sciences at the University of California, San Francisco, the Benjamin Rush Award Lecture, "The Great Neurosis: Clinical Constructions of Hysteria, 1876–1895"; Elissa P. Benedek, M.D., APA President-Elect and director of training and research at the Center for Forensic Psychiatry in Ann Arbor, "Sexual Harassment in the Workplace"; William W. Meissner, M.D., university professor of psychoanalysis at Boston College and training and supervising analyst at the Boston Psychoanalytic Institute, the Oskar Pfister Award Lecture, "The Pathology of Belief Systems"; and Hagop S. Akiskal, M.D., professor of psychiatry and director of the section of affective disorders at the University of Tennessee in Memphis, the Samuel G. Hibbs Award Lecture, "Chronic Depressions: Subtypes and Management."

The lectures presented on Thursday, May 11, were the following: John J. Hopfield, Ph.D., Roscoe Gilkey Dickinson professor of chemistry and biology at the California Institute of Technology, "Neural Networks: Simple Aspects of 'Mind' and 'Brain' in Physics"; Roger Peele, M.D., chairman of the psychiatry department, chief clinical officer, and director of the office of training and standards for the Washington, D.C., Commission on Mental Health Services, the Administrative Psychiatry Award Lecture, "Can the Public Psychiatric Administrator Be Ethical?"; Eva King Killam, Ph.D., editor-in-chief of the *Journal of Pharmacology and Experimental Therapeutics* and professor of pharmacology at the University of California, Davis, School of Medicine, "Chronic Psychotropic Drug Treatment: Potential Toxicity to Learning and Memory"; and Armistead Maupin, humorist and author, "Mondo Homo."

Other Activities

The Committee on Local Arrangements, Kathleen Bell Unger, M.D., and Mel I. Blaustein, M.D., co-chairpersons, planned many activities, among which were a "fun run," golf and tennis tournaments, birdwatching, and bicycling in Golden Gate Park. Some of the tours included: Sights of San Francisco, A Day of Tasting Napa's Finest, De Young Museum, Bay Cruise, and shopping on "Riviera by the Bay."

Meeting of the Board of Trustees

The Board of Trustees met in regular session on Sunday, May 7.

Meetings of the Assembly

The Assembly met on Friday, Saturday, and Sunday, May 5, 6, and 7.

PHILIP M. MARGOLIS, M.D.
Secretary, American Psychiatric Association

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Norpramin®

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BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

INACTIVE INGREDIENTS

The following inactive ingredients are contained in all dosage strengths: acacia, calcium carbonate, corn starch, D&C Red No. 30 and D&C Yellow No. 10 (except 10 mg and 150 mg), FD&C Blue No. 1, FD&C Red No. 3, FD&C Yellow No. 6, hydrogenated soy oil, iron oxide, light mineral oil, magnesium stearate, mannitol, polyethylene glycol 8000, pregelatinized corn starch, sodium benzoate (except 150 mg), sucrose, talc, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Metabolism

The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. In general, the elderly metabolize tricyclic antidepressants more slowly than do younger adults.

Certain drugs, particularly the psychostimulants and the phenothiazines, increase plasma levels of concomitantly administered tricyclic antidepressants through competition for the same metabolic enzyme systems. Other substances, particularly barbiturates and alcohol, induce liver enzyme activity and thereby reduce tricyclic antidepressant plasma levels. Similar effects have been reported with tobacco smoke.

Additional information on metabolism appears in Full Prescribing Information.

CONTRAINDICATIONS

Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS

1. Extreme caution should be used when this drug is given in the following situations:
   a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction.
   b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug.
   c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias.
   d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold.
2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds.
3. **USE IN PREGNANCY**
   Safe use of desipramine hydrochloride during pregnancy and lactation has not been established, therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive.
4. **USE IN CHILDREN**
   Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. (See ADVERSE REACTIONS, Cardiovascular.)
5. The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
6. In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS

1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly.
2. If serious adverse effects occur, dosage should be reduced or treatment should be altered.
3. Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates.
4. The drug may cause exacerbation of psychosis in schizophrenic patients.
5. Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs.
6. Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated.
7. Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered.
8. If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin.
9. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma levels of the tricyclic antidepressants. Conversely, decreases in plasma levels of the tricyclic antidepressants have been reported upon discontinuation of cimetidine which may result in the loss of the therapeutic efficacy of the tricyclic antidepressant.
10. This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride.
11. Both elevation and lowering of blood sugar levels have been reported.
12. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression.

ADVERSE REACTIONS

Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. There has been a report of an "acute collapse" and "sudden death" in an eight-year old (18 kg) male, treated for two years for hyperactivity. (See WARNINGS, Use in Children.)

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, painful ejaculation, testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

OVERDOSAGE

There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug.

Within an hour of ingestion the patient may become agitated or stuporous and then comatose. Hypotension, shock, and renal shutdown may ensue. Grand mal seizures, both early and late after ingestion, have been reported. Hyperactive reflexes, hyperpyrexia, muscle rigidity, vomiting, and ECG evidence of impaired conduction may occur. Serious disturbances of cardiac rate, rhythm, and output can occur. The precepts of early evacuation of the ingested material and subsequent support of respiration (airway and movement), circulation, and renal output apply.

The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure, and regulation of fluid and acid-base balance are well known in most medical centers and are not further discussed here.

Because CNS involvement, respiratory depression, and cardiac arrhythmia can occur suddenly, hospitalization and close observation are generally advisable, even when the amount ingested is thought to be small or the initial degree of intoxication appears slight or moderate. Most patients with ECG abnormalities should have continuous cardiac monitoring for at least 72 hours and be closely observed until well after cardiac status has returned to normal; relapses may occur after apparent recovery.

The slow intravenous administration of physostigmine salicylate has been reported to reverse most of the anticholinergic cardiovascular and CNS effects of overdose with tricyclic antidepressants. In adults, 1 to 3 mg has been reported to be effective. In children, the dose should be started with 0.5 mg and repeated at 5-minute intervals to determine the minimum effective dose; no more than 2 mg should be given. Because of the short duration of action of physostigmine, the effective dose should be repeated at 30-minute to 60-minute intervals, as necessary. Rapid injection should be avoided to reduce the possibility of physostigmine-induced convulsions.

Other possible therapeutic considerations include:

(a) Dialysis: Desipramine is found in low concentration in the serum, even after a massive oral dose. In vitro experiments in which blood bank blood was used indicate that it is very poorly dialyzed. Because of indications that the drug is secreted in gastric juice, constant gastric lavage has been suggested.

(b) Pharmacologic treatment of shock: Since desipramine potentiates the action of such vasopressor agents as levarterenol and metaraminol, they should be used only with caution.

(c) Pharmacologic control of seizures: Intravenous barbiturates are the treatment of choice for the control of grand mal seizures. One may, alternatively, consider the parenteral use of diphenylhydantoin, which has less central depressant effect but also has an effect on heart rhythm that has not yet been fully defined.

(d) Pharmacologic control of cardiac function: Severe disturbances of cardiac rate, rhythm, and output are probably the initiating events in shock. Intravascular volume must be maintained by i.v. fluids. Digitalization should be carried out early in view of the fact that a positive inotropic effect can be achieved without increase in cardiac work. Many of the cardiodynamic effects of digitalis are the exact opposite of those of massive doses of desipramine (animal studies).

Product Information as of January, 1989 Y398D

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Information for Contributors

GENERAL POLICIES

The requirements stated below are in accordance with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

Prior Publication

Manuscripts are accepted for consideration by the *American Journal of Psychiatry* with the understanding that they represent original material, have not been published previously, are not being considered for publication elsewhere, and have been approved by each author. Any form of publication other than an abstract of no more than 400 words constitutes prior publication. This includes components of symposia, proceedings, transactions, books (or chapters), articles published by invitation, or reports of any kind, regardless of differences in readership, as well as electronic data bases of public nature. Authors submitting manuscripts containing data or clinical observations already used in published papers or used in papers that are in press, submitted for publication, or to be submitted shortly should provide this information and copies of those papers to the Editor. An explanation of the differences between the papers should be included.

Copyright Transfer and Submission Approval

The *Journal* requires approval of manuscript submission by all authors in addition to transfer of copyright to the American Psychiatric Association so that the author(s) and the Association are protected from misuse of copyrighted material. A submission approval and copyright transfer form will be forwarded to authors along with a letter acknowledging receipt of their manuscript. Manuscripts will not receive a final decision until a completed form has been received in the editorial office.

In addition, authors must obtain letters of permission from publishers for use of extensive quotations (more than 500 words). The *Journal* does not publish tables or figures that have been previously published or submitted elsewhere.

Disclosure of Commercial Interests

All forms of support, including drug company support, must be acknowledged in the author's footnote (see "Acknowledgments" under the Title Page section). Also, authors must disclose in their cover letter any commercial or financial involvements that might present an appearance of a conflict of interest in connection with the submitted article, including but not limited to institutional or corporate affiliations not already specified in the author's footnote, paid consultancies, stock ownership or other equity interests, and patent ownership. At the Editor's discretion, this information may be shared with reviewers. Such involvements will not be grounds for automatic rejection of the manuscript. Should the article be accepted for publication, the Editor and the authors will consult on whether, and to what extent, this information should be included in the published article.

Patient Anonymity

Ethical as well as legal considerations require careful attention to the protection of a patient's anonymity in case reports and elsewhere. Identifying information such as names, initials, hospital numbers, and dates must be avoided. In addition, authors should disguise identifying information when discussing the characteristics and personal history of patients.

Informed Consent

Manuscripts that report the results of experimental investigation with human subjects must include a statement that informed consent was obtained after the procedure(s) had been fully explained. In the case of children, authors are asked to include information about whether the child's assent was obtained.

Review Process

All papers are reviewed to determine the originality, validity, and importance of content and conclusions. In addition to the regular review process, peer review for statistical content may be required for some manuscripts. This will be determined by the *Journal*'s Statistical Editors. Authors will be sent reviewer comments that are judged to be useful to them. All reviewers remain anonymous. Once the Editor has made a final decision on a paper, the authors of that paper will be informed.

SUBMISSION OF MANUSCRIPTS

The original manuscript and four copies should be submitted to John C. Nemiah, M.D., Editor, *American Journal of Psychiatry,* 1400 K St., N.W., Washington, DC 20005. All correspondence will be sent to the first-named author unless otherwise specified. Papers should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the *Journal* it is being submitted (i.e., Special Article, Regular Article, or Clinical and Research Report); papers will only be reviewed after such a statement has been received from the author.

Authors will be notified of the receipt of their paper and the number assigned to it. **This number must be included in all further correspondence.** It is imperative that the corresponding author of submitted papers notify the *Journal* of changes of address. Because of escalating postage costs, no manuscripts submitted to the *Journal* will be returned to authors except upon special request. Authors must make this request in their original submission letter and include a self-addressed, postage-paid envelope.

Single Case Reports

Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. All single case reports will be peer reviewed. Reports of successfully treated patients must include data on the number of patients treated unsuccessfully by the same method, with an indication of the temporal order of the successes and failures.

Annual Meeting Papers

Authors may submit their papers before the annual meeting, but such papers cannot be published until after the meeting. All papers must be accompanied by a statement that they are in final form. These papers are subject to the same peer review as other papers and must conform to the requirements for one of the types of articles specified in the next section.

TYPES OF ARTICLES

Special Articles

These are usually overview articles that bring together important information on a topic of general interest to psychiatry. Authors who have ideas for such articles are advised to check with the Editorial Office to ensure that a similar work has not already been submitted. Special Articles may not exceed 7,500 words (no more than 25 double-spaced pages—including an abstract of no more than 100 words, tables, and figures) and may not include more than 100 references.

Regular Articles

Regular Articles are original communications of scientific excellence in psychiatric medicine and advances in clinical research. Regular Articles contain no more than 3,800 words, including an abstract of no more than 100 words, references, tables, and figures. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. Articles that exceed 3,800 words will be returned unreviewed to the authors.

Clinical and Research Reports

Clinical and Research Reports may contain no more than one table and a maximum of 10 references; figures may not be used. Papers may contain a **maximum** of 1,300 words, including an abstract of no more than 40 words, references, and an optional table (estimate 15 words per reference, 100 words for a double-spaced table that fills one-half of a vertical page, and 150 words for a double-spaced table that fills one-half of a horizontal page). These articles present 1) new research findings, 2) data from pilot studies, 3) worthwhile replication studies, and 4) clinical studies involving a number of patients. Essays, program descriptions, literature reviews, and single case reports do not meet the criteria for this section. Submissions that exceed 1,300 words or contain figures will be returned to the author.

Other Sections

Letters to the Editor. Brief letters (maximum of 500 words and 5 references; no tables or figures) will be considered if they include the notation "for publication." Letters critical of an article published in the *Journal* will automatically be sent to the authors for reply. Because of space limitations not all letters can be printed. The *Journal* will notify authors about the disposition of their letters but does not return those that are not published. A letter must be signed by all of its authors. All letters will be edited; edited letters will not be sent to authors for approval. Letters must be typed **double-spaced** throughout on 8½×11 inch paper; three copies are required. Letters that do not meet these specifications will be returned for revision. Reprints are not available. **Single case reports except for detailed longitudinal studies should be submitted as Letters to the Editor. Case reports submitted as Letters to the Editor will be peer reviewed.**

Book Forum. Books for review may be sent to the Book Forum Editor, Nancy C. Andreasen, M.D., Ph.D., University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242. Book reviews are usually solicited by the Book Forum Editor. Authors interested in reviewing a particular book should communicate directly with Dr. Andreasen. Reprints of reviews are not available.

TYPING AND ARRANGING THE PAPER

All parts of the manuscript, including case reports, quotations, references, and tables, must be **double-spaced** throughout. Manuscripts must be typed in upper- and lowercase on one side only of 8½×11 inch **nonerasable** bond paper. All four margins must be 1½ inches. The manuscript should be arranged in the following order, with each item beginning a new page: 1) title page, 2) abstract, 3) text, 4) references, and 5) tables and/or figures. All pages must be numbered.

STYLE SPECIFICATIONS

Title Page

Title. The title should be informative and as brief as possible. Two-part titles should be avoided.

By-line. Authors listed in the by-line should be limited to principal researchers and/or writers; collaborators may be acknowledged in a footnote. Authors' first names are preferred to initials. Degrees should be included after each author's name.

Previous presentation. If the paper has been presented at a meeting, please give the name of the meeting, the place, and the date.

Location of work and address for reprints. Provide the department, institution, city, and state **where the work was done.** Include a full address for the author who is to receive reprint requests.

Acknowledgments. Grant support should be acknowledged in a separate paragraph and should include the full name of the granting agency and grant number. The *Journal* does not allow acknowledgment of persons involved with the preparation or typing of manuscripts. Acknowledgment of individuals involved with the scientific content of the work should not exceed four typed lines. Drug company support of any kind must be acknowledged.

Abstract

The abstract is a single paragraph no longer than 100 words for Special Articles and Regular Articles and no longer than 40 words for Clinical and Research Reports.

Text

Authors should use the active voice and first person; headings and subheadings should be inserted at reasonable intervals. Footnotes to text may not be used, and summaries are usually unnecessary.

Research design and statistics. The following information regarding research design should be included: 1) a clearly stated hypothesis, 2) the names of the statistical tests used, 3) whether tests were one- or two-tailed, and 4) what test was used for each set of data. Reporting of standard deviations, rather than standard errors of the mean, is required. Statistical tests that are not well known should be referenced. All significant and important nonsignificant results must include the test value, degree(s) of freedom, and probability. For example, "The analysis of variance indicated that those who abstained from coffee had significantly higher course grades than those who did not abstain ($F=4.32$, $df=3, 17$, $p<0.05$)." Reviewers will evaluate the appropriateness of the analyses.

Abbreviations. Spell out all abbreviations (other than those for units of measure) the first time they are used. Idiosyncratic abbreviations should not be used.

Drugs. Generic rather than trade names of drugs should be used. Trade or manufacturers' names are used only if the drug or equipment is experimental or unavailable in this country or if such information is crucial to the evaluation of the results or replication of the study.

References

References are numbered and listed by their order of appearance in text; the text citation is followed by the appropriate reference number in parentheses. Do **not** arrange the list alphabetically. References in tables and figures are numbered as though the tables and figures were part of the text.

References should be restricted to closely pertinent material. **Accuracy of citation is the author's responsibility.** References should conform exactly to the original spelling, accents, punctuation, etc. Authors should be sure that all references listed have been cited in text.

Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in text. It is the author's responsibility to obtain permission to refer to another individual's unpublished observations. Manuscripts that are actually "in press" may be cited as such in the reference list; the name of the journal or publisher and location must be included.

Type references in the style shown below, **double-spaced throughout.** List up to three authors; designate one or more authors past the third as "et al." Abbreviations of journal names should conform to the style used in *Index Medicus*; journals not indexed there should not be abbreviated.

1. Noyes R Jr, DuPont RL Jr, Pecknold JC, et al: Alprazolam in panic disorder and agoraphobia, results from a multicenter trial, II: patient acceptance, side effects, and safety. Arch Gen Psychiatry 1988; 45:423–428
2. Kaplan HI, Sadock BJ (eds): Comprehensive Textbook of Psychiatry, 4th ed, vol 2. Baltimore, Williams & Wilkins, 1985
3. Fyer AJ, Manuzza S, Endicott J: Differential diagnosis and assessments of anxiety: recent developments, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven Press, 1987

TABLES AND FIGURES

The *Journal* does not publish tables or figures that have been submitted elsewhere or previously published. Tables and figures that duplicate 1) material contained in text or 2) each other will not be used. Authors will be asked to delete tables and figures that contain data which could be given succinctly in text. Each table and figure should be understandable without reference to the text; a descriptive, concise title should be included and units of measurement should be specified. Consult recent issues of the *Journal* for format. A table or figure that fills one-half of a vertical manuscript page equals 100 words of text; one that fills one-half of a horizontal page equals 150 words. **A copy of each table and figure must be included with each copy of the manuscript.**

Tables

Tables should be double-spaced, no wider than 120 typewriter characters, including spaces, and no longer than 70 lines. Values expressed in the same unit of measurement should read down, not across; when percentages are given, the appropriate numbers must also be given.

Figures

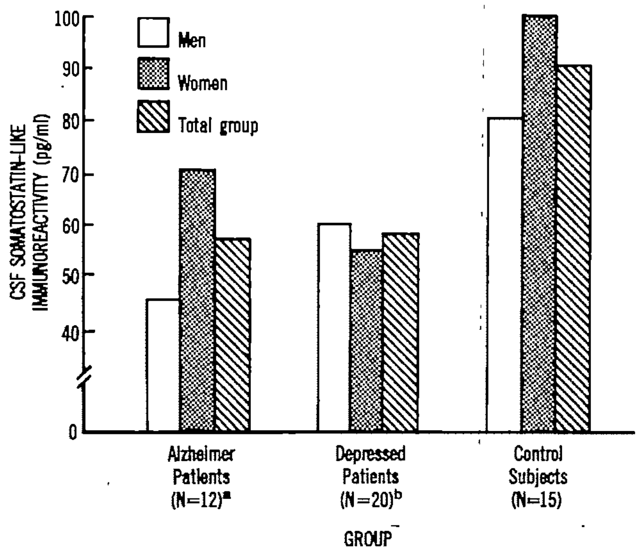
Figures are considered as text and are subject to revision by the authors upon recommendation of the Editors. Figures should, however, be professionally prepared. Glossy or other camera-ready prints should accompany the submitted manuscript. Computer-generated figures that do not meet quality printing standards will be returned for revision. The first author's name, the title of the paper, the figure number, and the top of the figure should be noted on a label affixed to the back of each figure. All figure titles and footnotes should be typed and sent together on a separate page.

The *Journal* does publish color illustrations. However, the cost to publish them, including reprint charges, will be the responsibility of the authors. An estimate of the cost will be provided to the authors at the time of first decision.

Format. Figures are visual expressions of data trends or relationships. Figures that represent numerical data which could be expressed more succinctly or clearly in tabular form should be converted to tables. Line graphs should show change in continuous variables; comparisons of like values in different groups should be presented as bar graphs. Graphs containing stacked bars are unacceptable; the different segments of each bar should be presented side by side.

Lettering. Figure type should be sans serif and should be 7 points or larger after the figure is reduced; most figures taking up the width of a vertical manuscript page are reduced to a width of 19.5 picas (3¼ inches), and those requiring a horizontal manuscript page are usually reduced to 40.5 picas (6¾ inches). When space on the horizontal axis is insuffi-

FIGURE 1. Mean CSF Somatostatin Levels of Patients With Alzheimer's Disease, Older Depressed Patients, and Age-Matched Control Subjects



[a] Significant difference between men and women (t=1.81, df=10, $p<0.05$) and between the total Alzheimer's disease group and the total control group (t=2.49, df=25, $p<0.01$).

[b] Significant difference between the total depressed group and the total control group (t=2.75, df=33, $p<0.005$).

cient, headings may be placed diagonally on the axis. Main headings should consist of upper-case letters only, subheadings of upper- and lower-case, and other type (e.g., keys, flow chart segments) of lower-case with only an initial upper-case letter. All parenthetical material should be lower-case. Do not use idiosyncratic abbreviations.

Other. The following are additional specific requirements. Please refer to the example given above.

1. Do not use solid black shading; rather, include outlined white among shadings.
2. The heading for the vertical axis of a graph should run vertically along the axis, not horizontally at the top or bottom. Headings for the horizontal axis should appear below that axis, not at the top of the graph.
3. Error bars should not be used.
4. Do not extend the vertical or horizontal axis of a graph beyond the point needed for the data shown.
5. The vertical axis should generally begin at zero; to save space, a double slash may take the place of an unused portion of the vertical axis.
6. In a graph comparing different groups of subjects, the number of subjects in each group should appear with the name of the group—in the key, in the headings below the horizontal axis, or in the title.
7. To save space, related figures that have the same vertical or horizontal axis should be combined. Headings identifying the segments of the combined figure should appear in the upper lefthand corners of the individual segments (in lower-case type with an initial upper-case letter).
8. The key should appear within or above the figure but should not be wider than the figure itself. Avoid placing other type (e.g., number of subjects, statistical values) within the axes of a graph.
9. Footnotes (including p values) should be cited with superscript letters in the title or body of the figure and should be listed in the order in which they are cited in the figure.

PROCESSING OF ACCEPTED MANUSCRIPTS

Manuscripts are accepted with the understanding that the Editor and the editorial staff have the right to make revisions aimed at greater conciseness, clarity, and conformity with *Journal* style. Accepted papers will be edited and sent to the first-named (or corresponding) author for corrections and answers to editorial queries. No proofs are sent to authors. Authors who will be away from their offices for a long period or who change address after notification of acceptance should inform the *Journal* staff.

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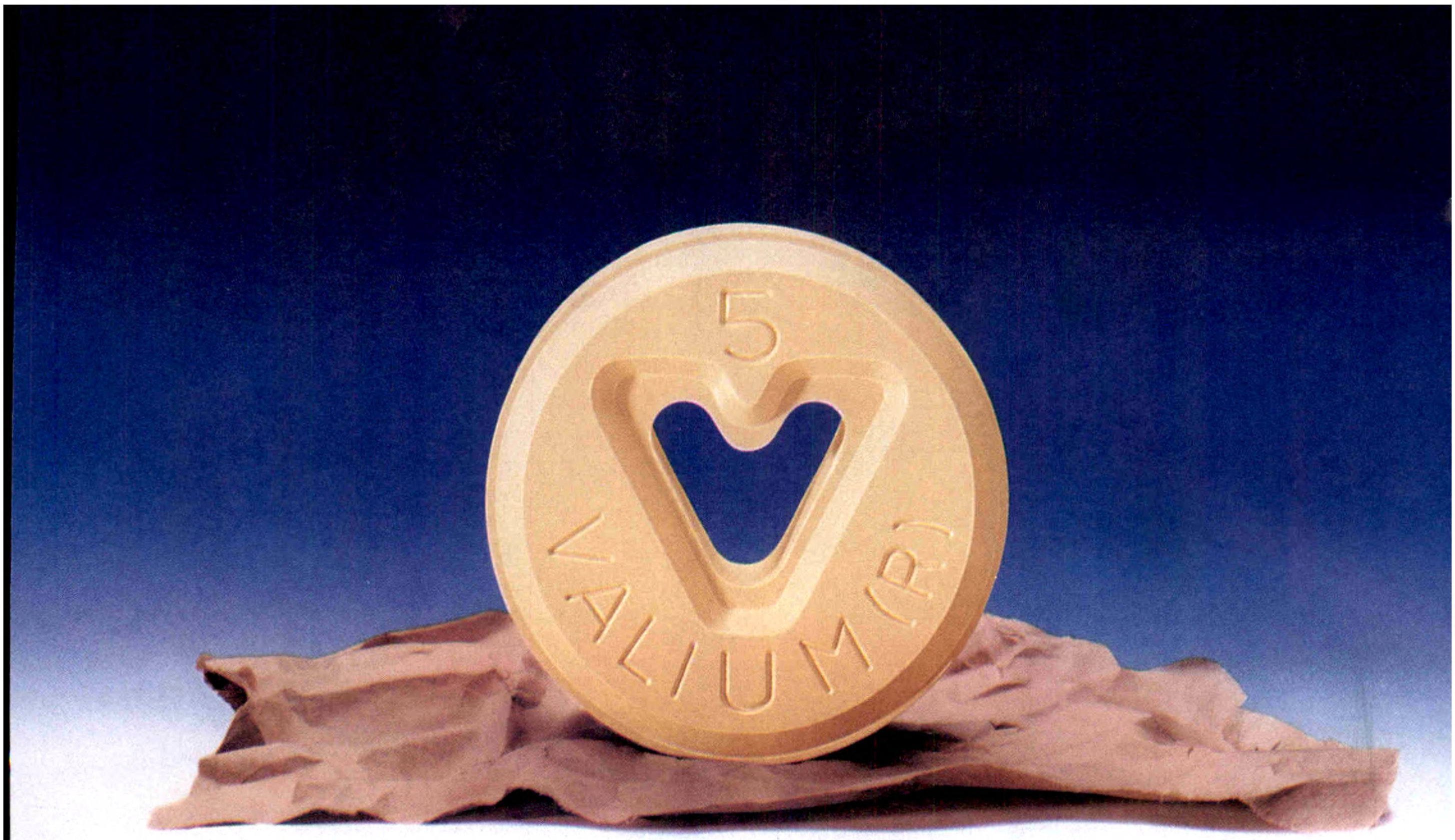
No Surprises



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As with any anxiolytic, patients should be cautioned against driving, operating machinery and the simultaneous ingestion of alcohol or other CNS depressant drugs.

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Please see a summary of product information on adjacent page.

VALIUM® (diazepam/Roche) Ⓒⅳ

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not as sole therapy).

The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATED: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

WARNINGS: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

PRECAUTIONS: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear. Inform patients to consult physician before increasing dose or abruptly discontinuing diazepam.

SIDE EFFECTS: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of diazepam; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. After extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

DOSAGE: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

HOW SUPPLIED: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow; 10 mg, blue—bottles of 100 and 500. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10.

P.I. 0788

Imprint on tablets:

2 mg—2 VALIUM® (front)
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ROCHE (scored side)

10 mg—10 VALIUM® (front)
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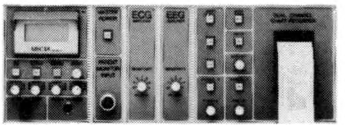
SR-1



JR-1

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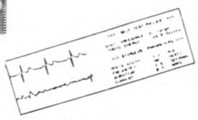

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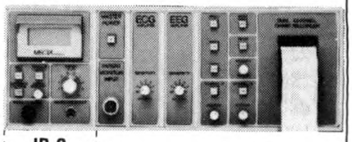
SR-2



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- Printed record of stimulus parameters
- Modular design for maximum flexibility

JR-2

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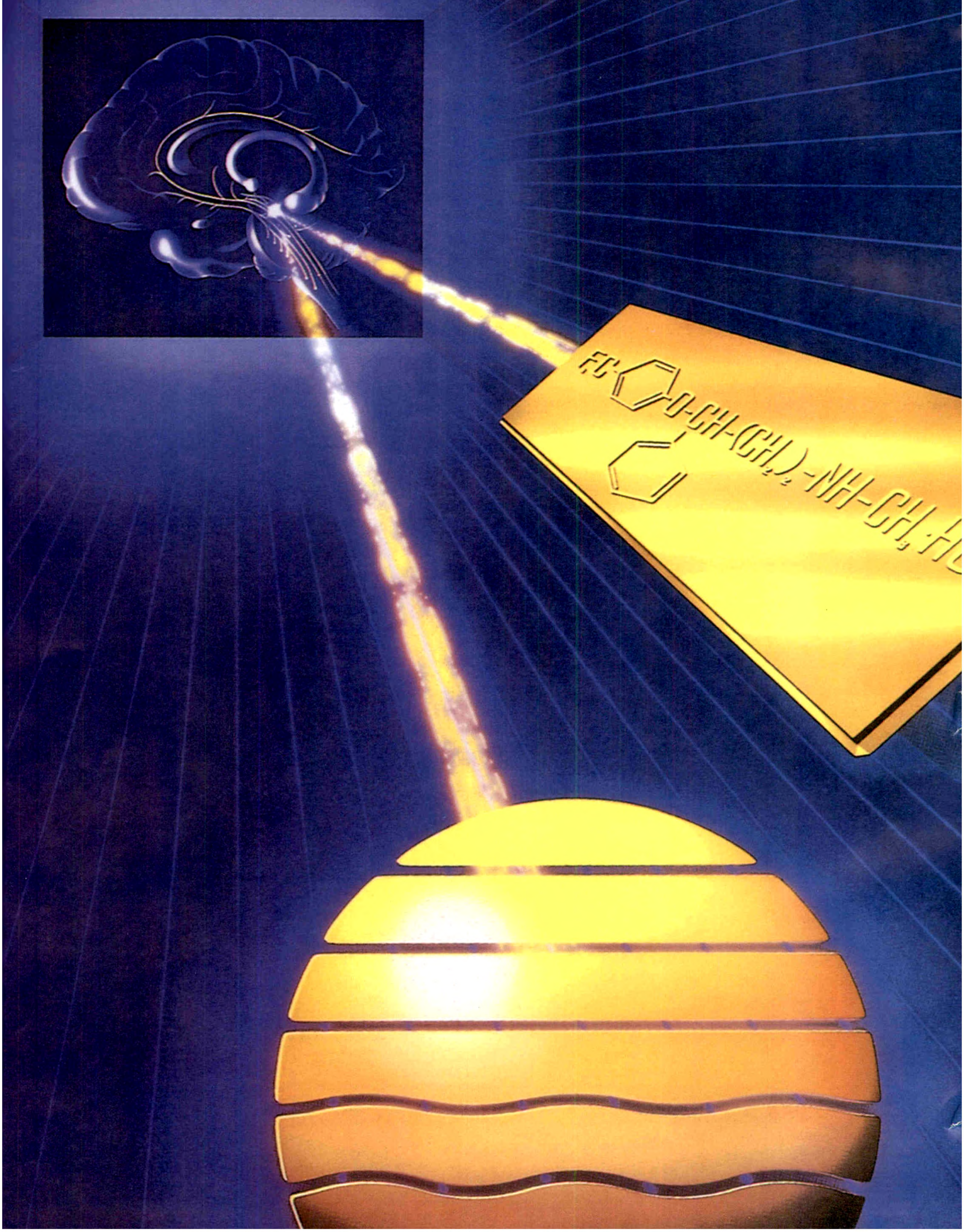
The synapse—crossroads for serotonin



In depression

PROZAC®

fluoxetine hydrochloride

"a potent serotonin reuptake inhibitor... represents a new class of antidepressants."[1]

Effectively relieves depression*

Unlike the tricyclics, Prozac specifically inhibits serotonin uptake. Its minimal action on other neurotransmitters may explain its favorable side-effect profile.

Fewer side effects to disrupt therapy

Side effects are generally mild and manageable, and include nausea, anxiety/nervousness, insomnia, and drowsiness

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Avoid using MAO inhibitors concomitantly or in proximity to Prozac

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Rash and/or urticaria occurred in 4% of clinical trial patients

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A wide margin of safety

20-mg once-a-day therapy

PROZAC...
A *specifically* different antidepressant

DISTA

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[1] *Curr Ther Res* 1986;39:559-563.
*As defined by DSM-III.

See adjacent page for brief summary of prescribing information.

FL-4907-T-949301

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Prozac®

fluoxetine hydrochloride

Brief Summary: Consult the package literature for complete prescribing information.

Indication: Prozac is indicated for the treatment of depression.

Contraindication: Prozac is contraindicated in patients known to be hypersensitive to it.

Warnings: *Monoamine Oxidase Inhibitors* – Data on the effects of the combined use of fluoxetine and MAO inhibitors are limited. Their combined use should be avoided. Based on experience with the combined administration of MAOIs and tricyclics, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with fluoxetine.

Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately five half-lives of norfluoxetine) should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI. Administration of an MAOI within five weeks of discontinuation of fluoxetine may increase the risk of serious events. While a causal relationship to fluoxetine has not been established, death has been reported to occur following the initiation of MAOI therapy shortly after discontinuation of fluoxetine.

Rash and Accompanying Events – During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Several other patients have had systemic syndromes suggestive of serum sickness.

Whether the association of rash and other events constitutes a true fluoxetine-induced syndrome, or a chance association of rash with the other signs and symptoms of different etiology or pathogenesis, is unknowable at this point in the drug's development.

Reassuring is the knowledge, cited above, that no patient is reported to have sustained lasting injury. Even though almost two thirds of those developing a rash continued to take fluoxetine without any consequence, the physician should discontinue Prozac upon appearance of rash.

Precautions: *General* – Anxiety and Insomnia – Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with Prozac. These symptoms led to drug discontinuation in 5% of patients treated with Prozac.

Altered Appetite and Weight – Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with Prozac.

In controlled clinical trials, approximately 9% of patients treated with Prozac experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with Prozac compared to 4% of placebo- and 3% of tricyclic-antidepressant-treated patients. However, only rarely have patients been discontinued from treatment with Prozac because of weight loss.

Activation of Mania/Hypomania – During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizures – Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2% that appears to be similar to that associated with other marketed antidepressants. Prozac should be introduced with care in patients with a history of seizures.

Suicide – The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

The Long Elimination Half-Lives of Fluoxetine and Its Metabolites – Because of the long elimination half-lives of the parent drug (two to three days) and its major active metabolite (seven to nine days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* Clinical Pharmacology *and* Dosage and Administration).

Use in Patients With Concomitant Illness – Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has **not** been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately three beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Interference With Cognitive and Motor Performance – Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients – Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests – There are no specific laboratory tests recommended.

Drug Interactions – As with all drugs, the potential for interaction by a variety of mechanisms (ie, pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc) is a possibility (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Tryptophan – Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine Oxidase Inhibitors – *See* Warnings.

Other Antidepressants – There have been greater than twofold increases of previously stable plasma levels of other antidepressants when Prozac has been administered in combination with these agents (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Diazepam Clearance – The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins – Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (eg, Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

CNS-Active Drugs – The risk of using Prozac in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Prozac and such drugs is required (*see* Accumulation and Slow Elimination *under* Clinical Pharmacology).

Electroconvulsive Therapy – There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. A single report of a prolonged seizure in a patient on fluoxetine has been reported.

Carcinogenesis, Mutagenesis, Impairment of Fertility – There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

The dietary administration of fluoxetine to rats and mice for two years at levels equivalent to approximately 7.5 and 9.0 times the maximum human dose (80 mg) respectively produced no evidence of carcinogenicity.

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Two fertility studies conducted in rats at doses of approximately five and nine times the maximum human dose (80 mg) indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted, but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Pregnancy – Teratogenic Effects – Pregnancy Category B – Reproduction studies have been performed in rats and rabbits at doses nine and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus due to Prozac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery – The effect of Prozac on labor and delivery in humans is unknown.

Nursing Mothers – It is not known whether and, if so, in what amount this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prozac is administered to a nursing woman.

Usage in Children – Safety and effectiveness in children have not been established.

Usage in the Elderly – Prozac has not been systematically evaluated in older patients; however, several hundred elderly patients have participated in clinical studies with Prozac, and no unusual adverse age-related phenomena have been identified. However, these data are insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Hyponatremia – Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Adverse Reactions: *Commonly Observed* – The most commonly observed adverse events associated with the use of Prozac and not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including anorexia, nausea, and diarrhea; and dizziness or lightheadedness.

Associated With Discontinuation of Treatment – Fifteen percent of approximately 4,000 patients who received Prozac in US premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety, and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

TABLE 1. TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Body System/ Adverse Event*	Percentage of Patients Reporting Event	
	Prozac (N=1,730)	Placebo (N=799)
Nervous		
Headache	20.3	15.5
Nervousness	14.9	8.5
Insomnia	13.8	7.1
Drowsiness	11.6	6.3
Anxiety	9.4	5.5
Tremor	7.9	2.4
Dizziness	5.7	3.3
Fatigue	4.2	1.1
Sedated	1.9	1.3
Sensation disturbance	1.7	2.0
Libido, decreased	1.6	–
Light-headedness	1.6	–
Concentration, decreased	1.5	–
Digestive		
Nausea	21.1	10.1
Diarrhea	12.3	7.0
Mouth dryness	9.5	6.0
Anorexia	8.7	1.5
Dyspepsia	6.4	4.3
Constipation	4.5	3.3
Pain, abdominal	3.4	2.9
Vomiting	2.4	1.3
Taste change	1.8	–
Flatulence	1.6	1.1
Gastroenteritis	1.0	1.4
Skin and Appendages		
Sweating, excessive	8.4	3.8
Rash	2.7	1.8
Pruritus	2.4	1.4
Body as a Whole		
Asthenia	4.4	1.9
Infection, viral	3.4	3.1
Pain, limb	1.6	1.1
Fever	1.4	–
Pain, chest	1.3	1.1
Allergy	1.2	1.1
Influenza	1.2	1.5
Respiratory		
Upper respiratory infection	7.6	6.0
Flu-like syndrome	2.8	1.9
Pharyngitis	2.7	1.3
Nasal congestion	2.6	2.3
Headache, sinus	2.3	1.8
Sinusitis	2.1	2.0
Cough	1.6	1.6
Dyspnea	1.4	–
Cardiovascular		
Hot flushes	1.8	1.0
Palpitations	1.3	1.4
Musculoskeletal		
Pain, back	2.0	2.4
Pain, joint	1.2	1.1
Pain, muscle	1.2	1.0
Urogenital		
Menstruation, painful	1.9	1.4
Sexual dysfunction	1.9	–
Frequent micturition	1.6	–
Urinary tract infection	1.2	–
Special Senses		
Vision disturbance	2.8	1.8

*Events reported by at least 1% of Prozac-treated patients are included.
– Incidence less than 1%.

Incidence in Controlled Clinical Trials – Table 1 enumerates adverse events that occurred at a frequency of 1% or more among Prozac-treated patients who participated in controlled trials comparing Prozac with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Other Events Observed During the Premarketing Evaluation of Prozac – During clinical testing in the US, multiple doses of Prozac were administered to approximately 5,600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (ie, reduced) number of standardized event categories.

In the tabulations which follow, a standard COSTART Dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 5,600 individuals exposed to Prozac who experienced an event of the type cited on at least one occasion while receiving Prozac. All reported events are included except those already listed in tables, those COSTART terms so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Prozac, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole – *Frequent:* chills; *Infrequent:* chills and fever, cyst, face edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, and pelvic pain; *Rare:* abdomen enlarged, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, and serum sickness.

Cardiovascular System – *Infrequent:* angina pectoris, arrhythmia, hemorrhage, hypertension, hypotension, migraine, postural hypotension, syncope, and tachycardia; *Rare:* AV block (first-degree), bradycardia, bundle-branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, and ventricular arrhythmia.

Digestive System – *Frequent:* increased appetite; *Infrequent:* aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, liver function tests abnormal, melena, stomatitis, and thirst; *Rare:* bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, hepatitis, hepatomegaly, hyperchlorhydria, increased salivation, jaundice, liver tenderness, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, and tongue edema.

Endocrine System – *Infrequent:* hypothyroidism; *Rare:* goiter and hyperthyroidism.

Hemic and Lymphatic System – *Infrequent:* anemia and lymphadenopathy; *Rare:* bleeding time increased, blood dyscrasia, leukopenia, lymphocytosis, petechia, purpura, sedimentation rate increased, and thrombocythemia.

Metabolic and Nutritional – *Frequent:* weight loss; *Infrequent:* generalized edema, hypoglycemia, peripheral edema, and weight gain; *Rare:* dehydration, gout, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemic reaction, hypokalemia, hyponatremia, and iron deficiency anemia.

Musculoskeletal System – *Infrequent:* arthritis, bone pain, bursitis, tenosynovitis, and twitching; *Rare:* bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, and rheumatoid arthritis.

Nervous System – *Frequent:* abnormal dreams and agitation; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, convulsion, delusions, depersonalization, emotional lability, euphoria, hallucinations, hostility, hyperkinesia, hypesthesia, incoordination, libido increased, manic reaction, neuralgia, neuropathy, paranoid reaction, psychosis, and vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagmus, paralysis, reflexes decreased, stupor, and torticollis.

Respiratory System – *Frequent:* bronchitis, rhinitis, and yawn; *Infrequent:* asthma, epistaxis, hiccup, hyperventilation, and pneumonia; *Rare:* apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/alveolitis, and pleural effusion.

Skin and Appendages – *Infrequent:* acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, and urticaria; *Rare:* eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, purpuric rash, pustular rash, seborrhea, skin discoloration, skin hypertrophy, subcutaneous nodule, and vesiculobullous rash.

Special Senses – *Infrequent:* amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, and tinnitus; *Rare:* blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, strabismus, and taste loss.

Urogenital System – *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, impotence, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, urination impaired, and vaginitis; *Rare:* abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metrorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, and vaginal hemorrhage.

Postintroduction Reports – Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and which may have no causal relationship with the drug include the following: vaginal bleeding after drug withdrawal, hyperprolactinemia, and thrombocytopenia.

Overdosage: *Human Experience* – As of December 1987, there were two deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs and/or alcohol. One death involved a combined overdose with approximately 1,800 mg of fluoxetine and an undetermined amount of maprotiline. Plasma concentrations of fluoxetine and maprotiline were 4.57 mg/L and 4.18 mg/L respectively. A second death involved three drugs yielding plasma concentrations as follows: fluoxetine, 1.93 mg/L; norfluoxetine, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took 3,000 mg of fluoxetine experienced two grand mal seizures that remitted spontaneously without specific anticonvulsant treatment (*see* Management of Overdose). The actual amount of drug absorbed may have been less due to vomiting.

Nausea and vomiting were prominent in overdoses involving higher fluoxetine doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation. Except for the two deaths noted above, all other overdose cases recovered without residua.

PV 2472 DPP [111788]

Additional information available to the profession on request from

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KUWAIT UNIVERSITY

Faculty of Medicine, Department of Psychiatry is seeking an Assistant or Associate Professor (Arabic speaking) for their teaching and clinical services. Applicants should have MRCPsych./American Board or equivalents. All teaching in the Faculty is in English. Academic expectations consist of teaching, research, and clinical contributions.

Salaries will be within the following scales according to qualifications and experience (1 KD = 2.3 St.Pounds, US$ 3.5 approximately). Increment per year KD.20/—.

Associate Professor: KD. 989—1149 (8 increments)
Assistant Professor: KD. 768— 928 (8 increments)

Other allowances

Social allowance will be paid as per the regulations and clinical allowance from the Ministry of Public Health for 10 months a year for clinical service commitments as follows:

Associate Professor: KD. 300/—
Assistant Professor: KD. 200/—

Other benefits

Conference attendance. Gratuity. Furnished accommodation (electricity and water free of charge). Free medical treatment in Kuwait. Free annual roundtrip airtickets from country of citizenship or permanent residence for self and family up to three dependent children. Baggage and freight allowance. Education fees for maximum three children in Kuwait from elementary through high school. No taxation. Currency is transferable without restriction. 60 days paid annual leave.

METHOD OF APPLICATION

Curriculum vitae in duplicate which should include the names of 3 referees; personal particulars; copy of the relevant pages of passport; qualifications with dates; career history; teaching experience, research accomplishments and, where appropriate clinical experience should be sent to:
THE VICE DEAN ADMINISTRATION (RECRUITMENT OFFICE), FACULTY OF MEDICINE, UNIVERSITY OF KUWAIT, P.O. BOX 24923 SAFAT, 13110, KUWAIT to arrive NO LATER THAN 31ST OCTOBER, 1989.

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Must be board-certified. Must have an Indiana license.

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Human Resources
Gary Community Mental Health Center Inc.
1100 WEST SIXTH AVENUE — GARY, INDIANA 46402 — (219) 881-2456
EOE/M/F

BILINGUAL PSYCHIATRISTS

Health Department Victoria, Australia

The Victorian Transcultural Psychiatry Unit (Office of Psychiatric Services, Health Department Victoria) has positions available for bilingual psychiatrists.

The responsibilities of the VTPU, which is located in central Melbourne, are:

- *Develop and provide bilingual psychiatric assessment treatment services and consultation/liaison services to OPS and other agencies.*
- *Develop research and teaching programs in the area of transcultural psychiatry.*
- *Provide interpreter services to OPS agencies. This is through the Mental Health Interpreter Service which has a staff of 11 and has been incorporated into the structure of the VTPU.*
- *Contribute to the formulation of OPS policy in relation to cultural/linguistic minorities.*

Melbourne has one of the most culturally and linguistically diverse populations in the world. The VTPU offers unusually exciting clinical research opportunities in development of effective, culturally appropriate psychiatric services for a culturally and linguistically plural society.

Requests for further information and applications (including curriculum vitae and the names, addresses and telephone numbers of three professional referees) may be sent to:

Dr Harry Minas
Victorian Transcultural Psychiatry Unit
Private Bag No 3
PARKVILLE VICTORIA 3052
AUSTRALIA
Telephone: (03) 389 2269
Facsimile: (03) 387 4273

Dr. Minas will be in Athens and London during October 1989 and would welcome the opportunity to discuss these positions with potential applicants.

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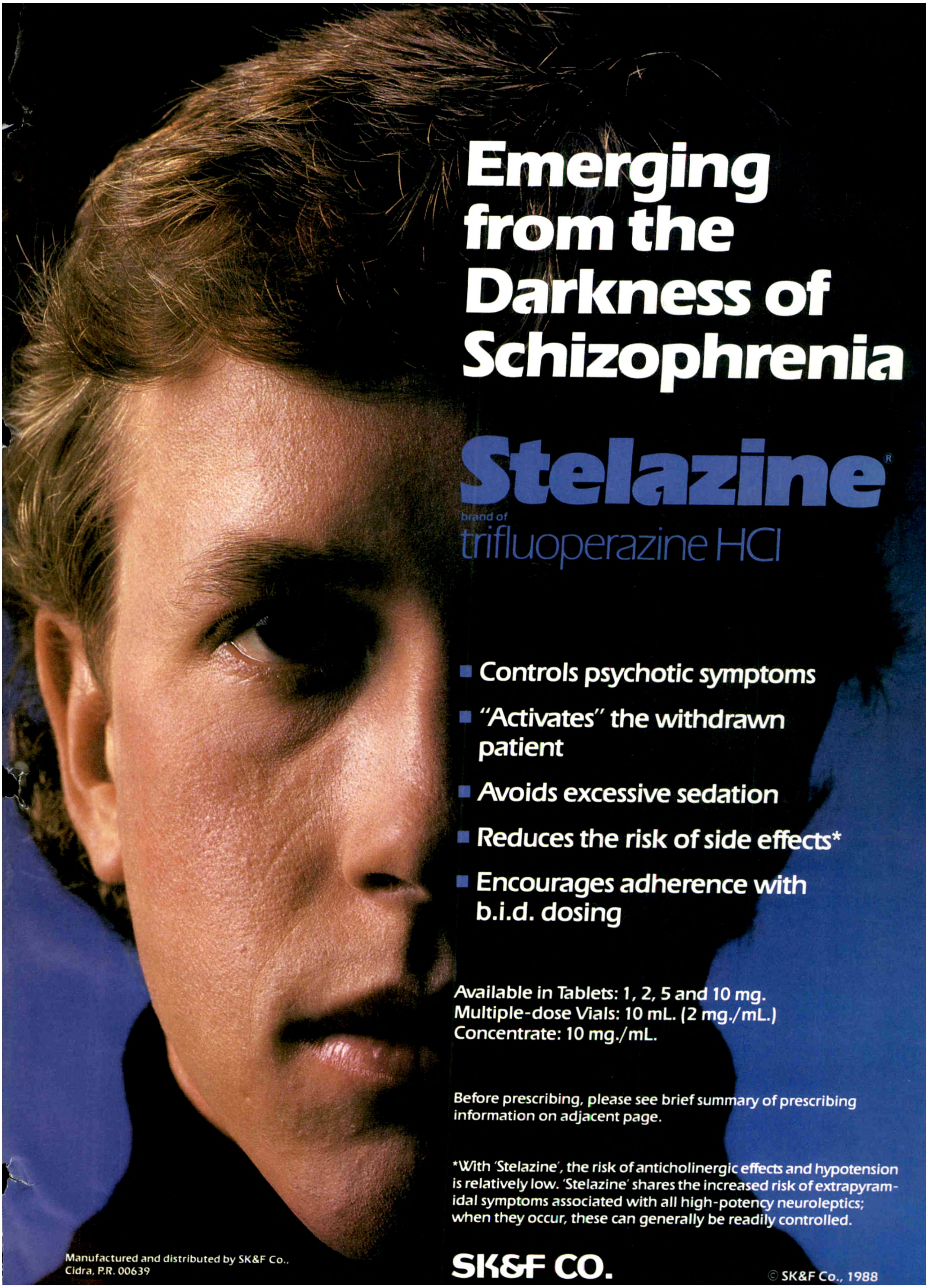

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*With 'Stelazine', the risk of anticholinergic effects and hypotension is relatively low. 'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics; when they occur, these can generally be readily controlled.

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Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations include: Hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment, if available, of any concomitant serious medical problems.

'Stelazine' Concentrate contains sodium bisulfite, which may cause allergic-type reactions including anaphylactic symptoms or asthmatic episodes in certain susceptible people. The prevalence of sulfite sensitivity in the general population is unknown and probably low and is seen more frequently in asthmatic than in non-asthmatic people.

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Chromosomal aberrations in spermatocytes and abnormal sperm have been demonstrated in rodents treated with certain neuroleptics. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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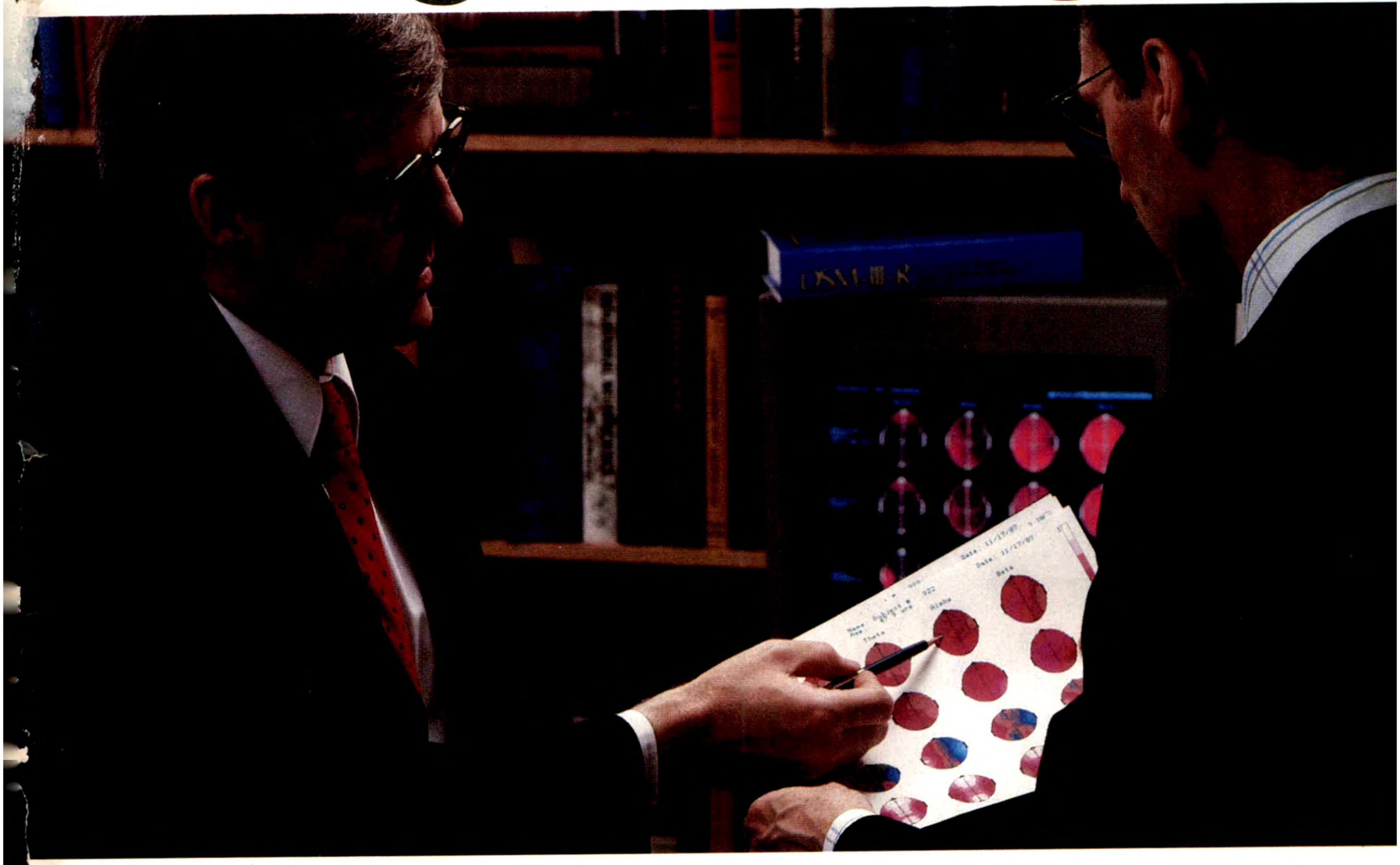

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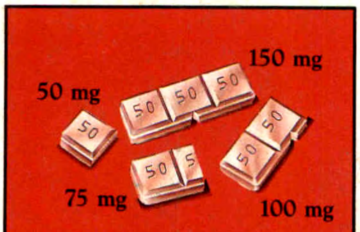

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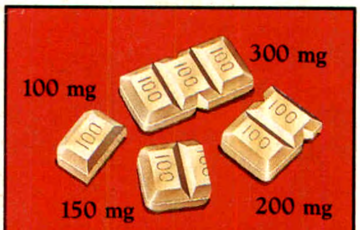

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